

FILED

JUN 18 2010

Clerk, U.S. District & Bankruptcy
Courts for the District of Columbia

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA**

Glaxo Group Limited, d/b/a GlaxoSmithKline
Glaxo Wellcome House
Berkeley Avenue
Greenford, Middlesex UB6 0NN
Great Britain

Plaintiff.

v.

HON. DAVID J. KAPPOS
Under Secretary of Commerce for Intellectual
Property and Director of the United States Patent
and Trademark Office
Office of General Counsel,
United States Patent and Trademark Office
P.O. Box 15667, Arlington, VA 22215
Madison Building East, Rm. 10B20
600 Dulany Street, Alexandria, VA 22314

Defendant.

Case: 1:10-cv-01032

Assigned To : Bates, John D.

Assign. Date : 6/18/2010

Description: Admn Agency Review

COMPLAINT

Plaintiff, Glaxo Group Limited, for its complaint against the Honorable David J. Kappos,
states as follows:

NATURE OF THE ACTION

1. This is an action by the assignee of United States Patent No. 7,635,701 ("the '701 patent") seeking judgment, pursuant to 35 U.S.C. §154(b)(4)(A), that the patent term adjustment for the '701 patent be changed from 550 days to at least 850 days.

2. This action arises under 35 U.S.C. §154 and the Administrative Procedures Act, 5 U.S.C. §§701-706.

JURISDICTION AND VENUE

3. This Court has jurisdiction to hear this action and is authorized to issue the relief sought pursuant to 28 U.S.C. §§1331, 1338(a), and 1361, 35 U.S.C. §154(b)(4)(A) and 5 U.S.C. §§701-706.

4. Venue is proper in this district by virtue of 35 U.S.C. §154(b)(4)(A).

5. This Complaint is timely filed in accordance with 35 U.S.C. §154(b)(4)(A).

THE PARTIES

6. Plaintiff Glaxo Group Limited, d/b/a GlaxoSmithKline, is a corporation organized under the laws of Great Britain, having a principal place of business at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB06 0NN, Great Britain.

7. Defendant David J. Kappos is the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office ("PTO"), acting in his official capacity. The Director is the head of the agency, charged by statute with providing management supervision for the PTO and for the issuance of patents. The Director is the official responsible for determining the period of patent term adjustment under 35 U.S.C. §154.

BACKGROUND

8. Andrew John Eatherton, Gerard Martin Paul Giblin, Richard Howard Green, Jennifer Margaret Daugherty, William Leonard Mitchell, Alan Naylor, Derek Anthony Rawlings, Brian Peter Slingsby and Andrew Richard Whittington are the inventors of the '701 patent, which issued on December 22, 2009, from U.S. Patent Application No. 10/524,470 ("the '470

application”) entitled “Pyrimidine Derivatives and Their Use as CB2 Modulators.” The ‘701 patent is attached as Exhibit A.

9. Plaintiff Glaxo Group Limited is the assignee of the ‘701 patent.

10. Section 154 of Title 35 of the United States Code requires that the Director of the PTO grant a patent term adjustment in accordance with the provisions of Section 154(b). Specifically, 35 U.S.C. §154(b)(3)(D) states that “[t]he Director shall proceed to grant the patent after completion of the Director’s determination of a patent term adjustment under the procedures established under this subsection, notwithstanding any appeal taken by the applicant of such determination.”

11. In determining patent term adjustment, the Director is required to extend the term of a patent for a period equal to the total number of days attributable to delay by the PTO under 35 U.S.C. §154(b)(1), as limited by any overlapping periods of delay by the PTO as specified under 35 U.S.C. §154(b)(2)(A), any disclaimer of patent term by the applicant under 35 U.S.C. §154(b)(2)(B) and any delay attributable to the applicant under 35 U.S.C. §154(b)(2)(C).

12. The Director made a determination of patent term adjustment pursuant to 35 U.S.C. §154(b)(3) and issued the ‘701 patent reflecting that determination.

13. 35 U.S.C. §154(b)(4)(A) provides that “[a]n applicant dissatisfied with a determination made by the Director under paragraph (3) shall have remedy by a civil action against the Director filed in the United States District Court for the District of Columbia within 180 days after grant of the patent. Chapter 7 of Title 5 shall apply to such an action.”

CLAIM FOR RELIEF

14. The allegations of paragraphs 1-13 are incorporated in this claim for relief as if fully set forth.

15. The patent term adjustment for the '701 patent, as determined by the Director under 35 U.S.C. §154(b) and indicated on the face of the '701 patent, is 550 days. (*See* Ex. A at page 1.) The determination of this patent term adjustment should be corrected because the PTO did not properly account for both the delays that occurred before the date that was three years after the actual filing of the '470 application (pursuant to 35 U.S.C. §154(b)(1)(A)) and the delay caused by the failure of the PTO to issue a patent within three years (pursuant to 35 U.S.C. §154(b)(1)(B)). The correct patent term adjustment for the '701 patent is at least 850 days.

16. The '470 application is a national stage filing under 35 U.S.C. §371 of international application number PCT/EP03/09217, filed August 19, 2003, which claims the benefit of priority of Great Britain application numbers 0219501.4, filed August 21, 2002 and 0309326.7, filed April 24, 2003. (*See* Ex. A at page 1.)

17. 35 U.S.C. §371 (b) and (f) define the actual filing date, or commencement, of a United States national stage application. According to 35 U.S.C. §371(b), the U.S. national stage commences on the date that is 30 months after the priority date of a Patent Cooperation Treaty ("PCT") application unless the applicant files an express request for early processing under 35 U.S.C. §371(f). Absent the filing of such a request, the U.S. national stage commences under the provisions of 35 U.S.C. §371(b).

18. Here, the 30-month period expired on February 21, 2005 and the national stage of the '470 application commenced on February 22, 2005, since no express request for early processing under 35 U.S.C. §371(f) was filed with the PTO.

19. On August 8, 2005, the PTO mailed Plaintiff a “Notification of Missing Requirements” under 35 U.S.C. §371, indicating that the inventor’s oath or declaration, in compliance with 37 C.F.R. 1.497(a) and (b), must be furnished to complete the requirements for acceptance under 35 U.S.C. §371.

20. This inventor’s oath or declaration was filed on February 28, 2006, thus satisfying all requirements for filing under 35 U.S.C. §371(c)(1), (2) and (4) (“the 371(c) completion date”). (*See* Ex. A at page 1.)

21. Under 35 U.S.C. §154(b)(1)(A), the applicant is guaranteed prompt PTO responses. If the issue of an original patent is delayed due to the failure of the PTO to engage in reasonable efforts to conclude prosecution, the term of the patent shall be extended in accordance with 37 C.F.R. § 1.703 (a) (“A Delay”): Here, the A Delay was calculated to be 527 days caused by the failure of the PTO to issue the first office action within 14 months from the 371(c) completion date.

22. Under 35 U.S.C. §154(b)(1)(B) and 37 C.F.R. §1.702(b), the applicant is guaranteed no more than a 3-year application pendency from the “actual filing date” of the application. Delay caused by the failure of the PTO to issue a patent within 3 years is assessed in accordance with 37 C.F.R. §1.703(b) (“B Delay”). The term of a patent shall be extended 1 day for each day after the end of that 3-year period until the patent is issued, not including any delay in the processing of the application requested by the applicant.

23. The starting date of the 3-year period is set forth in 35 U.S.C. §371(b): “Subject to subsection (f) of this section, the national stage shall commence with the expiration of the applicable time limit under article 22(1) or (2) or under article 39(1) of the [PCT].” According to the above, the actual filing date of the ‘470 application was the expiration of the 30-month period

(February 22, 2005) and the 3-year pendency ended on February 22, 2008. The total B Delay is the period beginning on February 22, 2008 and ending on the date the patent issued (December 22, 2009), which is 669 days

24. Under 35 U.S.C. §154(b)(2)(C), the number of days of applicant delay is 119 days.

25. 35 U.S.C. §154(b)(2)(A) provides that “to the extent that periods of delay attributable to grounds specified in paragraph [b](1) overlap, the period of any adjustment ... shall not exceed the actual number of days the issuance of the patent was delayed.” The overlap between the “A Delay” period (ending October 6, 2008) and the “B Delay” period (beginning February 22, 2008) in the prosecution of the ‘701 patent is 227 days.

26. The ‘701 patent is not subject to a disclaimer of term. Thus, the period of patent term adjustment is not limited under 35 U.S.C. §154(b)(2)(B).

27. Accordingly, the correct patent term adjustment under 35 U.S.C. §154(b)(1) and (2) is the sum of the “A Delay” and “B Delay” ($527 + 669 = 1196$) reduced by the number of days of applicant delay (119 days) and overlap period (227 days) for a net adjustment of 850 days.

28. The Director calculated the “B Delay” as having commenced on the actual filing date of the ‘470 application instead of as having commenced on the day that was three years after the actual filing date of the ‘470 application. As a result, the Director incorrectly determined that the entire period of “B Delay” overlapped with the entire period of “A Delay.”

29. Thus, the net patent term adjustment should not have been limited under 35 U.S.C. §154(b)(2)(A) to 550 days. Rather, the net patent term adjustment should have been 850 days.

30. In *Wyeth v. Kappos*, No. 2009-1120 (Fed. Cir., Jan. 7, 2010), the Federal Circuit affirmed this Court's explanation of the proper construction of the provisions of 35 U.S.C. §154(b) for determining patent term adjustment. In accordance with *Wyeth*, the patent term adjustment for the '701 patent is properly determined to be 850 days, as set forth above.

31. The determination that the '701 patent is entitled to only 550 days of patent term adjustment is arbitrary, capricious, an abuse of discretion or otherwise not in accordance with the law and in excess of statutory jurisdiction, authority or limitation.

PRAYER FOR RELIEF

Wherefore, Plaintiff demands judgment against Defendant and respectfully requests that this Court enter Orders:

A. Changing the period of patent term adjustment for the '701 patent term from 550 days to 850 days and requiring the Director to extend the term of the '701 patent to reflect the 850-day patent term adjustment.

B. Granting such other and future relief as the nature of the case may admit or require and as may be just and equitable.

Dated: June 18, 2010

Respectfully submitted,



Edmund J. Haughey, II (DC Bar No. 462773) ✓
FITZPATRICK, CELLA, HARPER & SCINTO
975 F Street, N.W.
Washington, DC 20004
Telephone: (202) 530-1010
Facsimile: (202) 530-1055
E-mail: ehaughey@fchs.com

Attorney for Plaintiff
Glaxo Group Limited, d/b/a GlaxoSmithKline

Of Counsel:

Colleen Tracy, Esq.
FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, NY 10104-3800
Telephone: (212) 218-2100
Facsimile: (212) 218-2200
E-mail: ctracy@fchs.com

Exhibit A



US007635701B2

(12) **United States Patent**
Eatherton et al.

(10) **Patent No.:** **US 7,635,701 B2**
(45) **Date of Patent:** **Dec. 22, 2009**

(54) **PYRIMIDINE DERIVATIVES AND THEIR USE AS CB2 MODULATORS**

(75) Inventors: **Andrew John Eatherton**, Welwyn (GB); **Gerard Martin Paul Gihlin**, Welwyn (GB); **Richard Howard Green**, Stevenage (GB); **Jennifer Margaret Doughty**, legal representative, Gorham, ME (US); **William Leonard Mitchell**, Welwyn (GB); **Alan Naylor**, Harlow (GB); **Derek Anthony Rawlings**, Welwyn (GB); **Brian Peter Slingsby**, Welwyn (GB); **Andrew Richard Whittington**, Stevenage (GB)

WO	WO 00/39101	7/2000
WO	WO 02/04429	1/2002
WO	WO 02/060447	8/2002
WO	WO 02/060447	8/2002
WO	WO 02/062750	8/2002
WO	WO 02/066036	8/2002
WO	WO 2004/000807	12/2003
WO	WO 2004/018433	3/2004
WO	WO 2004/018434	3/2004
WO	WO 2004/029026	4/2004
WO	WO 2004/029027	4/2004
WO	WO 2004/029204	4/2004
WO	WO 2004/002964	8/2004
WO	WO 2004/085385	10/2004

OTHER PUBLICATIONS

(73) Assignee: **Glaxo Group Limited**, Greenford, Middlesex (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 550 days.

(21) Appl No.: **10/524,470**

(22) PCT Filed: **Aug. 19, 2003**

(86) PCT No.: **PCT/EP03/09217**

§ 371 (c)(1).

(2), (4) Date: **Feb. 28, 2006**

(87) PCT Pub. No.: **WO2004/018433**

PCT Pub. Date: **Mar. 4, 2004**

(65) **Prior Publication Data**

US 2006/0293354 A1 Dec 28, 2006

(30) **Foreign Application Priority Data**

Aug. 21, 2002	(GB)	0219501.4
Apr. 24, 2003	(GB)	0309326.7

(51) **Int. Cl.**
C07D 239/42 (2006 01)
A61K 31/505 (2006.01)

(52) **U.S. Cl.** 514/275; 544/330; 544/331

(58) **Field of Classification Search** 544/330, 544/331; 514/275

See application file for complete search history

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,112,820 A	5/1992	Ward et al
5,811,428 A	9/1998	Suto et al
5,925,768 A	7/1999	Barth et al
6,107,301 A	8/2000	Aldrich et al
6,184,237 B1	2/2001	Mantlo et al

FOREIGN PATENT DOCUMENTS

EP	0569912	11/1993
EP	0576357	12/1993
FR	2839718	11/2003
WO	WO 97/09315	3/1997

Souness, J.E. "Immunosuppressive And Anti-inflammatory Effect of Cyclic AMP" Immunopharmacology, 2000, 47/2-3: 127-162

Huang, Z., et al "Next Generation of PDE4 Inhibitors" Current Opinion in Chemical Biology, 2001, pp. 432-438.

Sullivan, R. W., et al 2-Chloro-4-(trifluoromethyl)pyrimidine-5-N-(3',5'-bis(trifluoromethyl)phenyl)-carboxamic Potent Inhibitor of NF-KB and AP-1-Mediated Gene Expression Identified Using Solution-Phase Combinatorial Chemistry. J Med Chem : 1998, 41, 413-419

Huffman, J.W. "The Search For Selective Ligands For The CB2 Receptor" Currently Pharmaceutical Design, Bentham Science Publishers, vol 6, No 13, 2000, pp 1323-1337

Gerard M.P. Gihlin et al; Discovery of 2-[(2,4-Dichlorophenyl)amino]-N-[(tetrahydro-2H-pyran-4-yl)methyl]-4-(trifluoromethyl)-5-pyrimidinecarboxamide, a Selective CB2 Receptor Agonist for the Treatment of Inflammatory Pain. J. Med Chem, 2007, 50, 2597-2600. American chemical society, USA

Hatzelmann, A. et al, "Anti-Inflammatory and Immunomodulatory Potential of the Novel PDE4 Inhibitor Roflumilast In Vitro". Journal of Pharmacology and Experimental Therapeutics, 2001; 297 (1), 267-279.

Iwamura H et al, "In vitro and in vivo pharmacological characterization of JTE-907, a novel selective ligand for cannabinoid CB2 receptor", Journal of Pharmacology and Experimental Therapeutics, 2001, 296(2): 420-425

Malan, T.P. et al, "CB2 Cannabinoid Receptor Agonists: Pain Relief Without Psychoactive Effects?", Current Opinion in Pharmacology, 2003; 3, 62-67

Van Der Mey M. et al : "Novel selective PDE4 inhibitors 3 In vivo antiinflammatory activity of a new series of N-substituted cis-tetra- and cis-hexahydrophthalazinones". Journal of Pharmacology and Experimental Therapeutics, 2001, 45(12), 2520-2525

Hohmann, A.G. et al ; "Spinal and Peripheral Mechanisms of Cannabinoid Antinociception: Behavioral, Neurophysiological and Neuroanatomical Perspectives". Chemistry and Physics of Lipids, 2002, 121, 173-190

Farquhar-Smith, W.P. et al, "Administration of Endocannabinoids Prevents a Referred Hyperalgesia Associated with Inflammation of the Urinary Bladder". Anesthesiology, 2001, 94, 507-513

(Continued)

Primary Examiner—Deepak Rao
(74) **Attorney, Agent, or Firm**—J. Scott Young

(57) **ABSTRACT**

The present invention relates to novel pyrimidine derivatives, pharmaceutical compositions containing these compounds and their use in the treatment of diseases, particularly pain, which diseases are caused directly or indirectly by an increase or decrease in activity of the cannabinoid receptor.

19 Claims, No Drawings

US 7,635,701 B2

Page 2

OTHER PUBLICATIONS

- Jaggari, S.I. et al., "The Anti-Hyperalgesic Actions of the Cannabinoid Anandamide and the Putative CB2 Receptor Agonist Palmitoylethanolamide in Visceral and Somatic Inflammatory Pain", *Pain*, 1998, 76, 189-199
- Kehl, L.J. et al., "A cannabinoid Agonist Differentially Attenuates Deep Tissue Hyperalgesia in Animal Models of Cancer and Inflammatory Muscle Pain", *Pain*, 2003, 103, 175-186
- Goya, P. et al., "Cannabinoids and Neuropathic Pain", *Mini Reviews in Medicinal Chemistry*, 2003, 3, 765-772
- Yao, B.B. et al., "In Vitro and In Vivo Characterization of A-796260 A Selective Cannabinoid CB2 Receptor Agonist Exhibiting Analgesic Activity in Rodent Pain Models", *British Journal of Pharmacology*, 2008, 153, 390-401
- Pertwee, R.G. et al., "Cannabinoid Receptors and Pain": *Progress in Neurobiology*, 2001, 63, 569-611
- Jhaveri, M.D. et al., "Cannabinoid CB2 Receptor-Mediated Antinociception in Models of Acute and Chronic Pain", *Molecular Neurobiology*, 2007, 36, 26-35
- Izzo, A.A. et al., "The Cannabinoid CB2 Receptor: A Good Friend in the Gut", *Neurogastroenterology Motility*, 2007, 19, 704-708
- Malan, T.P. et al., "Inhibition of Pain Responses By Activation of CB2 Cannabinoid Receptors", *Chemistry and Physics of Lipids*, 2002, 121, 191-200

US 7,635,701 B2

1

PYRIMIDINE DERIVATIVES AND THEIR USE AS CB2 MODULATORS

CROSS REFERENCES TO RELATED APPLICATIONS

This application is a 371 Application of PCT/EP2003/009217, filed 19 Aug. 2003, which claims priority to GB Application Serial No. 0219501.4, filed 21 Aug. 2002 and 0309326.7, filed 24 Apr. 2003.

The present invention relates to novel pyrimidine derivatives, pharmaceutical compositions containing these compounds and their use in the treatment of diseases, particularly pain, which diseases are caused directly or indirectly by an increase or decrease in activity of the cannabinoid receptor.

Cannabinoids are a specific class of psychoactive compounds present in Indian *cannabis* (*Cannabis sativa*), including about sixty different molecules, the most representative being cannabinal, cannabidiol and several isomers of tetrahydrocannabinol. Knowledge of the therapeutic activity of *cannabis* dates back to the ancient dynasties of China, where, 5000 years ago, *cannabis* was used for the treatment of asthma, migraine and some gynaecological disorders. These uses later became so established that, around 1850, *cannabis* extracts were included in the US Pharmacopoeia and remained there until 1947.

Cannabinoids are known to cause different effects on various systems and/or organs, the most important being on the central nervous system and on the cardiovascular system. These effects include alterations in memory and cognition, euphoria, and sedation. Cannabinoids also increase heart rate and vary systemic arterial pressure. Peripheral effects related to bronchial constriction, immunomodulation, and inflammation have also been observed. The capability of cannabinoids to reduce intraocular pressure and to affect respiratory and endocrine systems is also well documented. See e.g. I. H. Hollister, *Health Aspects of Cannabis, Pharmacological Reviews*, Vol. 38, pp. 1-20, (1986). More recently, it was found that cannabinoids suppress the cellular and humoral immune responses and exhibit anti-inflammatory properties. Wirth et al., *Anti-inflammatory Properties of Cannabinochrome, Life Science*, Vol. 26, pp. 1991-1995, (1980).

In spite of the foregoing benefits, the therapeutic use of *cannabis* is controversial, both due to its relevant psychoactive effects (causing dependence and addiction), and due to manifold side effects that have not yet been completely clarified. Although work in this field has been ongoing since the 1940's, evidence indicating that the peripheral effects of cannabinoids are directly mediated, and not secondary to a CNS effect, has been limited by the lack of receptor characterisation, the lack of information concerning an endogenous cannabinoid ligand and, until recently, the lack of receptor sub-type selective compounds.

The first cannabinoid receptor was found to be mainly located in the brain, in neural cell lines, and, only to a lesser extent, at the peripheral level. In view of its location, it was called the central receptor ("CB1"). See Matsuda et al., "Structure of a Cannabinoid Receptor and Functional Expression of the Cloned cDNA," *Nature*, Vol. 346, pp. 561-564 (1990). The second cannabinoid receptor ("CB2") was identified in the spleen, and was assumed to modulate the non psychoactive effects of the cannabinoids. See Munro et al., "Molecular Characterization of a Peripheral Receptor for Cannabinoids," *Nature*, Vol. 365, pp. 61-65 (1993).

Recently, some compounds have been prepared which are capable of acting as agonists on both the cannabinoid receptors. For example, use of derivatives of dihydroxypyrrrole-1,

2

2,3-d.e)-1,4-benzoxazine in the treatment of glaucoma and the use of derivatives of 1,5-diphenyl-pyrazole as immunomodulators or psychotropic agents in the treatment of various neuropathologies, migraine, epilepsy, glaucoma, etc are known. See U.S. Pat. No. 5,112,820 and EP 576357, respectively. However, because these compounds are active on both the CB1 and CB2 receptor, they can lead to serious psychoactive effects.

The foregoing indications and the preferential localisation of the CB2 receptor in the immune system confirms a specific role of CB2 in modulating the immune and anti-inflammatory response to stimuli of different sources.

The total size of the patient population suffering from pain is vast (almost 300 million), dominated by those suffering from back pain, osteo-arthritic pain and post-operative pain.

Neuropathic pain (associated with neuronal lesions such as those induced by diabetes, HIV, herpes infection, or stroke) occurs with lower, but still substantial prevalence, as does cancer pain.

The pathogenic mechanisms that give rise to pain symptoms can be grouped into two main categories:

those that are components of inflammatory tissue responses (Inflammatory Pain).

those that result from a neuronal lesion of some form (Neuropathic Pain).

Chronic inflammatory pain consists predominantly of osteo-arthritis, chronic low back pain and rheumatoid arthritis. The pain results from acute and on-going injury and/or inflammation. There may be both spontaneous and provoked pain.

There is an underlying pathological hypersensitivity as a result of physiological hyperexcitability and the release of inflammatory mediators which further potentiate this hyperexcitability. CB2 receptors are expressed on inflammatory cells (T cells, B cells, macrophages, mast cells) and mediate immune suppression through inhibition of cellular interaction/inflammatory mediator release. CB2 receptors may also be expressed on sensory nerve terminals and therefore directly inhibit hyperalgesia.

The role of CB2 in immunomodulation, inflammation, osteoporosis, cardiovascular, renal and other disease conditions is now being examined. In light of the fact that cannabinoids act on receptors capable of modulating different functional effects, and in view of the low homology between CB2 and CB1, the importance of developing a class of drugs selective for the specific receptor sub-type is evident. The natural or synthetic cannabinoids currently available do not fulfil this function because they are active on both receptors.

Based on the foregoing, there is a need for compounds which are capable of selectively modulating the receptor for cannabinoids and, therefore, the pathologies associated with such receptors. Thus, CB2 modulators offer a unique approach toward the pharmacotherapy of immune disorders, inflammation, osteoporosis, renal ischemia and other pathological conditions.

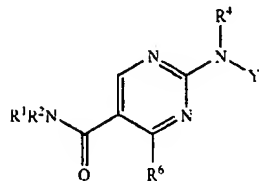
The present invention provides novel pyrimidine derivatives of formula (I) and pharmaceutically acceptable derivatives thereof, pharmaceutical compositions containing these compounds or derivatives, and their use as CB2 receptor modulators, which are useful in the treatment of a variety of disorders.

The present invention further comprises a method for treating disease mediated by CB2 receptors in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

US 7,635,701 B2

3

The invention provides compounds of formula (I)



wherein

Y is phenyl, optionally substituted with one, two or three substituents:

R¹ is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl and halosubstituted C₁₋₆ alkyl;

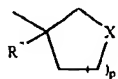
R² is (CH₂)_mR³ where m is 0 or 1;

or R¹ and R² together with N to which they are attached form an optionally substituted 4 to 8-membered non-aromatic heterocyclyl ring;

R³ is an optionally substituted 4- to 8-membered non-aromatic heterocyclyl group, an optionally substituted C₃₋₈ cycloalkyl group, an optionally substituted straight or branched C₁₋₁₀ alkyl, a C₅₋₇ cycloalkenyl or R⁵;

R⁴ is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or halosubstituted C₁₋₆ alkyl, COCH₃, and SO₂Me;

R⁵ is



wherein p is 0, 1 or 2 and X is CH₂ or O,

R⁶ is methyl, chloro or CHxF_n wherein n is 1, 2, or 3, x is 0, 1 or 2 and n and x add up to 3;

R⁷ is OH, C₁₋₆alkoxy, NR^{8a}R^{8b}, NHCOR⁹, NHSO₂R⁹, SOqR⁹;

R^{8a} is H or C₁₋₆alkyl;

R^{8b} is H or C₁₋₆alkyl;

R⁹ is C₁₋₆alkyl;

q is 0, 1 or 2;

and pharmaceutically acceptable derivatives thereof.

In one particular embodiment Y is a substituted phenyl.

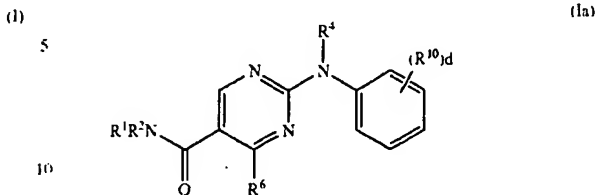
In one particular embodiment Y is substituted by 1 or 2 substituents. If mono-substituted, in one particular embodiment the substituent is in the 3 position. If di-substituted, in one particular embodiment the substituents are in the 2- and 4-positions.

When Y is substituted, the substituent or substituents are preferably selected from C₁₋₆ alkyl, halosubstituted C₁₋₆ alkyl, C₁₋₆ alkoxy, a hydroxy group, a cyano group, halo, a C₁₋₆alkylsulfonyl group, —CONH₂, —NHC(=O)CH₃ and —COOH. Furthermore the substituent or substituents can be selected from halosubstituted C₁₋₆alkoxy, and SO₂NR^{8a}R^{8b} wherein R^{8a} and R^{8b} are as defined above. Additionally the substituent or substituents can be SC₁₋₆alkyl.

In one particular embodiment Y is substituted by chloro, fluoro, bromo, cyano, CF₃, methyl, CF₃O— or SCH₃ and methoxy; more particularly halo, cyano or methoxy.

4

In one particular embodiment the compound of formula (I) is a compound of formula (Ia)



wherein:

R¹ is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl and halosubstituted C₁₋₆ alkyl;

R² is (CH₂)_mR³ where m is 0 or 1;

or R¹ and R² together with N to which they are attached form a 4- to 8-membered non-aromatic ring selected from azetidiny, pyrrolidiny, morpholinyl, piperizinyl, piperidinyl, tetrahydropyridiny, azapine, oxapine, azacyclooctanyl, azaoxacyclooctanyl and azathiacyclooctanyl any of which can be unsubstituted or substituted by one, two or three substituents selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, a hydroxy group, a cyano group, halo, sulfonyl group, methylsulfonyl, NR^{8a}R^{8b}, NHC(=O)CH₃, (=O), and —CONHCH₃;

R³ is 2- or 3-azetidiny, oxetanyl, thioxetanyl, thioxetanyl-s-oxide, thioxetanyl-s-s-dioxide, dioxalanyl, pyrrolidinyl, tetrahydrofuranly, tetrahydrothiophenyl, morpholinyl, piperidinyl, piperizinyl, tetrahydropyranly, tetrahydrothiopyranly, thiomorpholinyl, thiomorpholinyl-s-s-dioxide, tetrahydropyridinyl, azapine, oxapine, azacyclooctanyl, azaoxacyclooctanyl, azathiacyclooctanyl, oxacyclooctanyl, thiacyclooctanyl, a C₃₋₈ cycloalkyl group, a straight or branched C₁₋₁₀ alkyl, a C₅₋₇ cycloalkenyl or R⁵, any of which can be unsubstituted or substituted by one, two or three substituents selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, a hydroxy group, a cyano group, halo, sulfonyl group, methylsulfonyl, NR^{8a}R^{8b}, NHC(=O)CH₃, (=O), and —CONHCH₃;

R¹⁰ is selected from C₁₋₆ alkyl, halosubstituted C₁₋₆ alkyl, C₁₋₆ alkoxy, a hydroxy group, a cyano group, halo, a C₁₋₆alkyl sulfonyl group, —CONH₂, —NHC(=O)CH₃, —COOH, halo-substituted C₁₋₆alkoxy, SC₁₋₆alkyl and SO₂NR^{8a}R^{8b};

R⁴ is selected from hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or halosubstituted C₁₋₆ alkyl, COCH₃, and SO₂Me;

R⁵ is



wherein p is 0, 1 or 2 and X is CH₂ or O;

R⁶ is methyl, chloro or CHxF_n wherein n is 1, 2, or 3, x is 0, 1 or 2 and n and x add up to 3;

R⁷ is OH, C₁₋₆alkoxy, NR^{8a}R^{8b}, NHCOR⁹, NHSO₂R⁹, SOqR⁹;

R^{8a} is H or C₁₋₆alkyl;

R^{8b} is H or C₁₋₆alkyl;

R⁹ is C₁₋₆alkyl;

q is 0, 1 or 2;

d is 0, 1, 2 or 3

and pharmaceutically acceptable derivatives thereof.

In one particular embodiment R¹ is hydrogen.

In one particular embodiment R⁴ is C₁₋₆alkyl or hydrogen, more preferably methyl or hydrogen even more preferably hydrogen.

US 7,635,701 B2

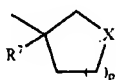
5

Alternatively R^1 and R^2 together with N to which they are attached form an optionally substituted 5- or 6-membered non-aromatic heterocyclyl ring.

When R^1 and R^2 together with N to which they are attached form a 4- to 8-membered non-aromatic heterocyclyl ring which is substituted, or when R^3 is substituted, the substituent or substituents are preferably selected from: C_{1-6} alkyl, C_{1-6} alkoxy, a hydroxy group, a cyano group, halo or a sulfonyl group. Additionally the optional substituent(s) can be chosen from methylsulfonyl, $NR^{8a}R^{8b}$, $NHCOCH_3$, $(=O)$, or $-CONHCH_3$.

In one particular embodiment R^6 is CH_2F , for example CF_3 , CHF_2 , CH_2F , more preferably CF_3 .

In one particular embodiment R^5 is



wherein p is 0, 1 or 2;

In one particular embodiment R^7 is OH.

In one particular embodiment R^3 is an optionally substituted 4- to 8-membered non-aromatic heterocyclyl group, an optionally substituted C_{3-8} cycloalkyl group, an optionally substituted straight or branched C_{1-10} alkyl or R^5 .

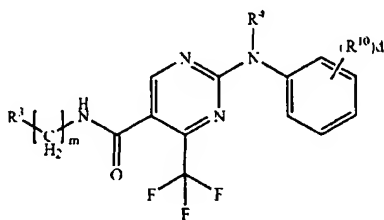
In one particular embodiment when R^3 is an optionally substituted C_{3-8} cycloalkyl group or an optionally substituted 4- to 8-membered nonaromatic heterocyclyl, m is 1.

In one particular embodiment R^3 is an optionally substituted C_{3-6} cycloalkyl group or an optionally substituted 4- or 6-membered nonaromatic heterocyclyl.

In one particular embodiment R^1 and R^2 together with N to which they are attached form a 4- to 8-membered non-aromatic heterocyclyl ring which is selected from pyrrolidinyl, morpholinyl, piperizinyl, piperidinyl and tetrahydropyridinyl.

In one particular embodiment when R^3 is nonaromatic heterocyclyl it is selected from pyrrolidinyl, tetrahydrofuran-yl, tetrahydrothiophenyl, morpholinyl, piperidinyl, piperazinyl, tetrahydropyran-yl, tetrahydrothiopyran-yl, thiomorpholinyl, thiomorpholinyl-s-s-dioxide, tetrahydropyridinyl.

In one particular embodiment the compound of formula (1) is a compound of formula (1b)



wherein:

R^3 is pyrrolidinyl, tetrahydrofuran-yl, tetrahydrothiophen-yl, morpholinyl, piperidinyl, piperazinyl, tetrahydropyran-yl, tetrahydrothiopyran-yl, thiomorpholinyl, thiomorpholinyl-s-s-dioxide, tetrahydropyridinyl, a C_{3-8} cycloalkyl group, any of which can be unsubstituted or substituted by one, two or three substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, a hydroxy group, a cyano group, halo, sulfonyl group, methylsulfonyl, $NR^{8a}R^{8b}$, $NHCOCH_3$, $(=O)$, and $-CONHCH_3$;

6

R^{10} is selected from chloro, fluoro, bromo, cyano, CF_3 , methyl, CF_3O- or SCH_3 and methoxy;

R^2 is selected from hydrogen or methyl;

R^{8a} is H or C_{1-6} alkyl;

R^{8b} is H or C_{1-6} alkyl;

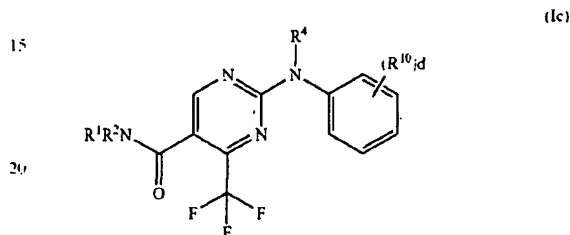
m is 0 or 1

d is 0, 1, 2 or 3 and

and pharmaceutically acceptable derivatives thereof.

In one particular embodiment m is 1.

In one particular embodiment the compound of formula (1) is a compound of formula (1c)



wherein;

R^1 and R^2 together with N to which they are attached form a 5- to 6-membered non-aromatic ring selected from pyrrolidinyl, morpholinyl, piperizinyl, piperidinyl and tetrahydropyridinyl, any of which can be unsubstituted or substituted by one, two or three substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, a hydroxy group, a cyano group, halo, sulfonyl group, methylsulfonyl, $NR^{8a}R^{8b}$, $NHCOCH_3$, $(=O)$, and $-CONHCH_3$.

R^{10} is selected from chloro, fluoro, bromo, cyano, CF_3 , methyl, CF_3O- or SCH_3 and methoxy;

R^4 is hydrogen or methyl;

R^{8a} is H or C_{1-6} alkyl;

R^{8b} is H or C_{1-6} alkyl;

d is 0, 1, 2 or 3 and

and pharmaceutically acceptable derivatives thereof.

In one particular embodiment the compounds are selective for CB2 over CB1. Preferably the compounds are 100 fold selective i.e. compounds of formula (1) have an EC50 value at the cloned human cannabinoid CB2 receptor of at least 100 times the EC50 values at the cloned human cannabinoid CB1 receptor or have less than 10% efficacy at the CB1 receptor.

The invention is described using the following definitions unless otherwise indicated.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of such ester or solvate of the compounds of formula (1), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (1) or an active metabolite or residue thereof.

It will be appreciated by those skilled in the art that compounds of formula (1) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds, and that the compounds of formula (1) may be derivatised at more than one position.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically acceptable salts, but other salts may find use, for example in the preparation of compounds of formula (1) and the physiological acceptable salts thereof. Pharmaceutically acceptable salts include those described by Berge, Bighley and Mondkhouse, J. Pharm. Sci., 1977, 66, 1-19. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable

US 7,635,701 B2

7

non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropyl amine, tromethamine, and the like. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like.

Preferred examples of pharmaceutically acceptable salts include the ammonium, calcium, magnesium, potassium, and sodium salts, and those formed from maleic, fumaric, benzoic, ascorbic, pantoic, succinic, hydrochloric, sulfuric, bis-methylenesalicylic, methanesulfonic, ethanedithionyl, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, cyclohexylsulfamic, phosphoric and nitric acids.

The terms 'halogen or halo' are used to represent fluorine, chlorine, bromine or iodine.

The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group or combinations thereof, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, pentyl, hexyl, 1,1-dimethylethyl, or combinations thereof.

The term 'alkoxy' as a group or as part of a group means a straight, branched or cyclic chain alkyl group having an oxygen atom attached to the chain, for example a methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy group, pentoxy, hexyloxy group, cyclopentoxy or cyclohexyloxy group.

The term 'cycloalkyl' means a closed non-aromatic ring, for example cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, or cyclooctyl.

The term 'cycloalkenyl' as a group or part of a group means a non-aromatic ring, containing at least one $\text{CH}=\text{CH}$ moiety for example cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl, or cyclooctenyl.

When R^1 and R^2 taken together with the N to which they are attached form an optionally substituted heterocyclyl ring, the ring may optionally contain 1, 2, 3 or 4 further heteroatoms. The ring may be saturated or unsaturated. Preferably the further heteroatoms are selected from oxygen, nitrogen or sulphur. An example of a 4-membered heterocyclyl ring is azetidiny. Examples of 5-membered heterocyclyl rings include pyrrolidiny. Examples of 6-membered heterocyclyl rings are morpholinyl, piperizinyl or piperidinyl. An additional example is tetrahydropyridiny. Examples of a 7-membered heterocyclyl ring are azapine or oxapine. Examples of 8-membered heterocyclyl rings are azacyclooctanyl, azaoxacyclooctanyl or azathiacyclooctanyl.

8

When R^3 is an optionally substituted non-aromatic heterocyclyl group, the ring may contain 1, 2, 3, or 4 heteroatoms. Preferably the heteroatoms are selected from oxygen, nitrogen or sulphur. Examples of 4-membered groups are 2- or 3-azetidiny, oxetanyl, thioxetanyl, thioxetanyl-s-oxide, thioxetanyl-s,s-dioxide. Examples of 5-membered heterocyclyl groups in this instance include dioxalanyl, pyrrolidiny or tetrahydrofuranyl or tetrahydrothiophenyl. Examples of 6-membered heterocyclyl groups are morpholinyl, piperidinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, thiomorpholinyl or thiomorpholinyl-s,s-dioxide. An additional example is tetrahydropyridiny. Examples of a 7-membered heterocyclyl ring are azapine or oxapine. Examples of 8-membered groups are azacyclooctanyl, azaoxacyclooctanyl or azathiacyclooctanyl, oxacyclooctanyl, or thiacyclooctanyl.

In one particular embodiment compounds of the present invention can be selected from:

- 1-[2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-piperidin-1-ylmethanone;
- 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclopentylmethyl-amide;
- 1-[2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholin-4-yl-methanone;
- 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide;
- 2-Phenylamino-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide;
- 1-[2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholin-4-yl-methanone;
- 1-[2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholin-4-yl-methanone;
- 1-[2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholin-4-yl-methanone;
- 1-[2-(2,5-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholin-4-yl-methanone;
- 1-[2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholin-4-yl-methanone;
- 1-[2-(3-Bromophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholin-4-yl-methanone;
- 1-[2-(3-Bromophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-piperidin-4-yl-methanone;
- 1-[2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholinyl-methanone;
- 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclopentylamide;
- 2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide;
- 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide;
- 2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide;
- 2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide;
- 2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide;
- 2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide;
- 2-(2,6-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide;
- 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide;
- 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidin-5-carboxylic acid cyclobutylamide;
- 2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide;

12

- [illegible]

US 7,635,701 B2

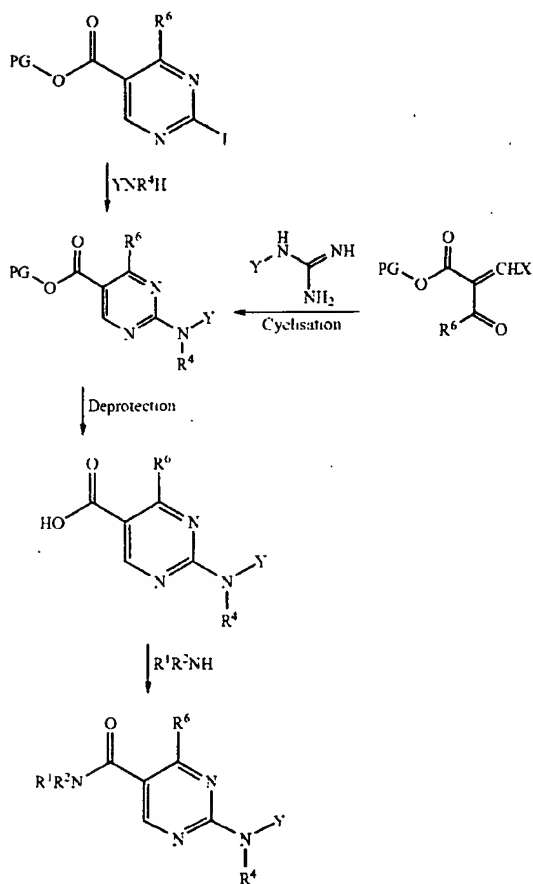
13

2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydrothiopyran-4-ylmethyl) amide.

and pharmaceutically acceptable derivatives thereof.

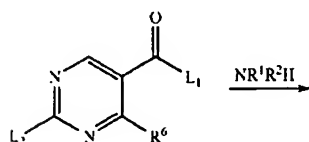
Compounds of formula (I) can be prepared as set forth in the following schemes:

Scheme 1

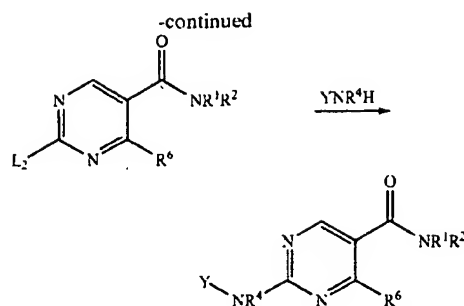


wherein L₁ is a leaving group, for example halo. PG is a protecting group for example methyl, ethyl or benzyl. X is a leaving group for example halo, OC₁₋₆alkyl, e.g. O-methyl or O-ethyl or NR^aR^b wherein R^a and R^b are independently selected from C₁₋₆alkyl, e.g. methyl, and R¹, R², R⁴, R⁶ and Y are as defined for compounds of formula (I).

Scheme 2



14



wherein L₁ and L₂ are leaving groups independently selected from halo, for example chloro, R¹, R², R⁴, R⁶ and Y are as defined for compounds of formula (I)

It is to be understood that the present invention encompasses all isomers of compounds of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses. The subject invention also includes isotopically-labeled compounds, which are identical to those recited in formulas I and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ³H, ¹¹C, ¹⁴C, ¹⁸F, ¹²³I and ¹²⁵I.

Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ³H, ¹⁴C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ³H, and carbon-14, i.e., ¹⁴C, isotopes are particularly preferred for their ease of preparation and detectability. ¹¹C and ¹⁸F isotopes are particularly useful in PET (positron emission tomography), and ¹²³I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ²H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of formula I and following of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

The compounds of formula (I) may be prepared in crystalline or noncrystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates or solvates as well as compounds containing variable amounts of water and/or solvent.

US 7,635,701 B2

15

The compounds of the invention bind selectively to the CB2 receptor, and are therefore useful in treating CB2 receptor mediated diseases.

In view of their ability to bind to the CB2 receptor, the compounds of the invention may be useful in the treatment of the disorders that follow. Thus, the compounds of formula (I) may be useful as analgesics. For example they may be useful in the treatment of chronic inflammatory pain (e.g. pain associated with rheumatoid arthritis, osteo-arthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis) including the property of disease modification and joint structure preservation; musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-cardiac dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain, headache; toothache; and dysmenorrhea.

The compounds of the invention may also be useful disease modification or joint structure preservation in multiple sclerosis, rheumatoid arthritis, osteo-arthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis.

The compounds of the invention may be particularly useful in the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of formula (I) may also be useful in the treatment of fever.

The compounds of formula (I) may also be useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis), ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varioliforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel dis-

16

ease, gastro esophageal reflux disease); organ transplantation; other conditions with an inflammatory component such as vascular disease, migraine, periarthritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, myaesthesia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, tendinitis, bursitis, and Sjogren's syndrome.

The compounds of formula (I) are also useful in the treatment of immunological diseases such as autoimmune diseases, immunological deficiency diseases or organ transplantation. The compounds of formula (I) are also effective in increasing the latency of HIV infection.

The compounds of formula (I) are also useful in the treatment of diseases of abnormal platelet function (e.g. occlusive vascular diseases).

The compounds of formula (I) are also useful for the preparation of a drug with diuretic action.

The compounds of formula (I) are also useful in the treatment of impotence or erectile dysfunction.

The compounds of formula (I) are also useful for attenuating the hemodynamic side effects of non-steroidal anti-inflammatory drugs (NSAID's) and cyclooxygenase-2 (COX-2) inhibitors.

The compounds of formula (I) are also useful in the treatment of neurodegenerative diseases and neurodegeneration such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions; trauma; infections and related conditions (including HIV infection); dementia in Parkinson's disease; metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment. The compounds may also be useful for the treatment of amyotrophic lateral sclerosis (ALS) and neuroinflammation.

The compounds of formula (I) are also useful in neuroprotection and in the treatment of neurodegeneration following stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

The compounds of formula (I) are also useful in the treatment of tinnitus.

The compounds of formula (I) are also useful in the treatment of psychiatric disease for example schizophrenia, depression (which term is used herein to include bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder, dysthymic disorders with early or late onset and with or without atypical features, neurotic depression and social phobia, depression accompanying dementia for example of the Alzheimer's type, schizoaffective disorder or the depressed type, and depressive disorders resulting from general medical conditions including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc), anxiety disorders (including generalised anxiety disorder and social anxiety disorder), panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder, memory disorders, including dementia, amnesic disorders and age-associated memory impairment, disorders of eating behaviours, including anorexia nervosa and bulimia nervosa, sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy).

US 7,635,701 B2

17

withdrawal from abuse of drugs such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine (phencyclidine-like compounds), opiates (e.g. *cannabis*, heroin, morphine), amphetamine or amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) or a combination thereof

The compounds of formula (I) are also useful in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence-inducing agent. Examples of dependence inducing agents include opioids (e.g. morphine), CNS depressants (e.g. ethanol), psycho-stimulants (e.g. cocaine) and nicotine.

The compounds of formula (I) are also useful in the treatment of kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), liver dysfunction (hepatitis, cirrhosis), gastrointestinal dysfunction (diarrhoea) and colon cancer.

It is to be understood that references to treatment includes both treatment of established symptoms and prophylactic treatment unless explicitly stated otherwise.

According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the activity of cannabinoid 2 receptors.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by the activity of cannabinoid 2 receptors which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

According to a further aspect of the invention we provide a method of treating a human or animal subject suffering from an immune disorder, an inflammatory disorder, pain, rheumatoid arthritis, multiple sclerosis, osteoarthritis or osteoporosis which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof. Preferably the pain is selected from inflammatory pain, visceral pain, cancer pain, neuropathic pain, lower back pain, muscular skeletal, post operative pain, acute pain and migraine. More preferably the inflammatory pain is pain associated with rheumatoid arthritis or osteoarthritis.

According to another aspect of the invention is provided the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment or prevention of a condition such as an immune disorder, an inflammatory disorder, pain, rheumatoid arthritis, multiple sclerosis, osteoarthritis or osteoporosis

Preferably the pain is selected from inflammatory pain, visceral pain, cancer pain, neuropathic pain, lower back pain, muscular skeletal, post operative pain, acute pain and migraine. More preferably the inflammatory pain is pain associated with rheumatoid arthritis or osteoarthritis.

In order to use a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. Therefore in another aspect of the invention is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine

18

As used herein, "modulator" means both antagonist, full or partial agonist and inverse agonist. In one embodiment of the present modulators are agonists.

The term "treatment" or "treating" as used herein includes the treatment of established disorders and also includes the prophylaxis thereof. The term "prophylaxis" is used herein to mean preventing symptoms in an already afflicted subject or preventing recurrence of symptoms in an afflicted subject and is not limited to complete prevention of an affliction

Compounds of formula (I) and their pharmaceutically acceptable derivatives may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, dermally, intranasally, transdermally, rectally, via inhalation or via buccal administration.

Compositions of formula (I) and their pharmaceutically acceptable derivatives which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or derivative in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of formula (I) or a pharmaceutically acceptable derivative thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.01 mg/Kg to 500 mg/Kg for example 0.1 mg to 500 mg/Kg, and preferably from 0.01 mg to 100 mg/Kg for example 1 mg/Kg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg/Kg, of a compound of formula (I) or a pharmaceutically acceptable derivative thereof calculated as the free acid. Each dosage unit for intranasal administration contains suit-

US 7,635,701 B2

19

ably 1400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 5.0% of a compound of formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg. of a compound of formula (I) or a pharmaceutically acceptable derivative thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg. of a compound of formula (I) or a pharmaceutically acceptable derivative thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

It may be advantageous to prepare the compounds of the present invention as nanoparticles. This may improve the oral bioavailability of the compounds. For the purposes of the present invention "nanoparticulate" is defined as solid particles with 50% of the particles having a particle size of less than 1 μ m, more preferably less than 0.75 μ m.

The particle size of the solid particles of compound (I) may be determined by laser diffraction. A suitable machine for determining particle size by laser diffraction is a Lecotrak laser particle size analyser, using an HELOS optical bench fitted with a QUIXEL dispersion unit.

Numerous processes for the synthesis of solid particles in nanoparticulate form are known. Typically these processes involve a milling process, preferably a wet milling process in the presence of a surface modifying agent that inhibits aggregation and/or crystal growth of the nanoparticles once created. Alternatively these processes may involve a precipitation process, preferably a process of precipitation in an aqueous medium from a solution of the drug in a non-aqueous solvent.

Accordingly, in a further aspect, the present invention provides a process for preparing compound (I) in nanoparticulate form as hereinbefore defined, which process comprises milling or precipitation.

Representative processes for the preparation of solid particles in nanoparticulate form are described in the patents and publications listed below.

U.S. Pat. No. 4,826,689 to Violante & Fischer. U.S. Pat. No. 5,145,684 to Liversidge et al. U.S. Pat. No. 5,298,262 to Na & Rajagopalan. U.S. Pat. No. 5,302,401 Liversidge et al. U.S. Pat. No. 5,336,507 to Na & Rajagopalan. U.S. Pat. No. 5,340,564 to Illig & Sarpotdar. U.S. Pat. No. 5,346,702 to Na Rajagopalan. U.S. Pat. No. 5,352,459 to Hollister et al. U.S. Pat. No. 5,354,560 to Lovrecich. U.S. Pat. No. 5,384,124 to Courteille et al. U.S. Pat. No. 5,429,824 to June. U.S. Pat. No. 5,503,723 to Ruddy et al. U.S. Pat. No. 5,510,118 to Bosch et al. U.S. Pat. No. 5,518 to Bruno et al. U.S. Pat. No. 5,518,738 to Eickhoff et al. U.S. Pat. No. 5,534,270 to De Castro. U.S. Pat. No. 5,536,508 to Canal et al. U.S. Pat. No. 5,552,160 to Liversidge et al. U.S. Pat. No. 5,560,931 to Eickhoff et al. U.S. Pat. No. 5,560,932 to Bagchi et al. U.S. Pat. No. 5,565,188 to Wong et al. U.S. Pat. No. 5,571,536 to Eickhoff et al. U.S. Pat. No. 5,573,783 to Desieno & Stetsko. U.S. Pat. No. 5,580,579 to Ruddy et al. U.S. Pat. No. 5,585,108 to Ruddy et al. U.S. Pat. No. 5,587,143 to Wong. U.S. Pat. No. 5,591,456 to Franson et al. U.S. Pat. No. 5,622,938 to Wong. U.S. Pat. No. 5,662,883 to Bagchi et al. U.S. Pat. No. 5,665,331 to Bagchi et al. U.S. Pat. No. 5,718,919 to Ruddy et al. U.S. Pat. No. 5,747,001 to Wiedmann et al. WO93/25190, WO96/24336, WO 97/14407, WO 98/35666, WO 99/65469, WO 00/18374, WO 00/27369, WO 00/30615 and WO 01/41760.

20

Such processes may be readily adapted for the preparation of compound (I) in nanoparticulate form. Such processes form a further aspect of the invention.

The process of the present invention preferably uses a wet milling step carried out in a mill such as a dispersion mill in order to produce a nanoparticulate form of the compound. The present invention may be put into practice using a conventional wet milling technique, such as that described in Lachman et al., *The Theory and Practice of Industrial Pharmacy*, Chapter 2, "Milling" p. 45 (1986).

In a further refinement, WO02/00196 (SmithKline Beecham plc) describes a wet milling procedure using a mill in which at least some of the surfaces are made of nylon (polyamide) comprising one or more internal lubricants, for use in the preparation of solid particles of a drug substance in nanoparticulate form.

In another aspect the present invention provides a process for preparing compounds of the invention in nanoparticulate form comprising wet milling a suspension of compound in a mill having at least one chamber and agitation means, said chamber(s) and/or said agitation means comprising a lubricated nylon, as described in WO02/00196.

The suspension of a compound of the invention for use in the wet milling is typically a liquid suspension of the coarse compound in a liquid medium. By "suspension" is meant that the compound is essentially insoluble in the liquid medium. Representative liquid media include an aqueous medium. Using the process of the present invention the average particle size of coarse compound of the invention may be up to 1 mm in diameter. This advantageously avoids the need to pre-process the compound.

In a further aspect of the invention the aqueous medium to be subjected to the milling comprises compound (I) present in from about 1% to about 40% w/w, preferably from about 10% to about 30% w/w, more preferably about 20% w/w.

The aqueous medium may further comprise one or more pharmaceutically acceptable water-soluble carriers which are suitable for steric stabilisation and the subsequent processing of compound (I) after milling to a pharmaceutical composition, e.g. by spray drying. Pharmaceutically acceptable excipients most suitable for steric stabilisation and spray-drying are surfactants such as poloxamers, sodium lauryl sulphate and polysorbates etc; stabilisers such as celluloses e.g. hydroxypropylmethyl cellulose; and carriers such as carbohydrates e.g. mannitol.

In a further aspect of the invention the aqueous medium to be subjected to the milling may further comprise hydroxypropylmethyl cellulose (HPMC) present from about 0.1 to about 10% w/w.

The process of the present invention may comprise the subsequent step of drying compound of the invention to yield a powder.

Accordingly, in a further aspect, the present invention provides a process for preparing a pharmaceutical composition containing a compound of the present invention which process comprises producing compound of formula (I) in nanoparticulate form optionally followed by drying to yield a powder.

A further aspect of the invention is a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof in which the compound of formula (I) or a pharmaceutically acceptable derivative thereof is present in solid particles in nanoparticulate form, in admixture with one or more pharmaceutically acceptable carriers or excipients.

By "drying" is meant the removal of any water or other liquid vehicle used during the process to keep compound of formula (I) in liquid suspension or solution. This drying step

US 7,635,701 B2

21

may be any process for drying known in the art, including freeze drying, spray granulation or spray drying. Of these methods spray drying is particularly preferred. All of these techniques are well known in the art. Spray drying/fluid bed granulation of milled compositions is carried out most suitably using a spray dryer such as a Mobile Minor Spray Dryer [Niro, Denmark], or a fluid bed drier, such as those manufactured by Glatt, Germany.

In a further aspect the invention provides a pharmaceutical composition as hereinbefore defined, in the form of a dried powder, obtainable by wet milling solid particles of compound of formula (I) followed by spray-drying the resultant suspension

Preferably, the pharmaceutical composition as hereinbefore defined, further comprises HPMC present in less than 15% w/w, preferably in the range 0.1 to 10% w/w.

The CB₂ receptor compounds for use in the instant invention may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, deracoxib, rofecoxib, valdecoxib, parecoxib or COX-189; 5-lipoxygenase inhibitors; NSAID's, such as aspirin, diclofenac, indomethacin, nabumetone or ibuprofen; leukotriene receptor antagonists, DMARD's such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA receptor modulators, such as glycine receptor antagonists; gabapentin and related compounds; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; 5HT₁ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; EP₁ receptor ligands, EP₄ receptor ligands; EP₂ receptor ligands; EP₃ receptor ligands; EP₄ antagonists; EP₂ antagonists and EP₃ antagonists; bradykinin receptor ligands and vanilloid receptor ligand, antirheumatoid arthritis drugs, for example anti TNF drugs e.g. enbrel, remicade, anti-IL-1 drugs, or DMARDS e.g. leflunomide. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

Additional COX-2 inhibitors are disclosed in U.S. Pat Nos. 5,474,995 5,633,272; 5,466,823, 6,310,099 and 6,291,523; and in WO 96/23405, WO 97/38986, WO 98/03484, WO 97/14691, WO99/12930, WO00/26216, WO00/52008, WO00/38311, WO01/58881 and WO02/18374.

The compound of the present invention may be administered in combination with other active substances such as 5HT₃ antagonists, NK-1 antagonists, serotonin agonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants and/or dopaminergic antidepressants.

Suitable 5HT₃ antagonists which may be used in combination of the compound of the inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compound of the invention include sumatriptan, rauwolfscine, yohimbine, metoclopramide.

Suitable SSRIs which may be used in combination with the compound of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

Suitable SNRIs which may be used in combination with the compound of the invention include venlafaxine and reboxetine.

22

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptyline, chlomipramine and nortriptyline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

It will be appreciated that the compounds of any of the above combinations or compositions may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

Determination of Cannabinoid CB1 Receptor Agonist Activity

The cannabinoid CB1 receptor agonist activity of the compounds of formula (I) was determined in accordance with the following experimental method

Experimental Method

Yeast (*Saccharomyces cerevisiae*) cells expressing the human cannabinoid CB1 receptor were generated by integration of an expression cassette into the ura3 chromosomal locus of yeast strain MMY23. This cassette consisted of DNA sequence encoding the human CB1 receptor flanked by the yeast GPD promoter to the 5' end of CB1 and a yeast transcriptional terminator sequence to the 3' end of CB1. MMY23 expresses a yeast/mammalian chimeric G-protein alpha subunit in which the C-terminal 5 amino acids of G_{pal} are replaced with the C-terminal 5 amino acids of human G_{ai3} (as described in Brown et al. (2000). Yeast 16:11-22). Cells were grown at 30°C. in liquid Synthetic Complete (SC) yeast media (Guthrie and Fink (1991). Methods in Enzymology, Vol. 194) lacking uracil, tryptophan, adenine and leucine to late logarithmic phase (approximately 6 OD₆₀₀/ml).

Agonists were prepared as 10 mM stocks in DMSO. EC₅₀ values (the concentration required to produce 50% maximal response) were estimated using dilutions of between 3- and 5-fold (BioMek iX, Beckman) into DMSO. Agonist solutions in DMSO (1% final assay volume) were transferred into black, clear bottom, microtitre plates from NUNC (96- or 384-well). Cells were suspended at a density of 0.2 OD₆₀₀/ml in SC media lacking histidine, uracil, tryptophan, adenine and leucine and supplemented with 10 mM 3-aminotriazole, 0.1M sodium phosphate pH 7.0, and 20 μM fluorescein di-β-D-glucopyranoside (FDGlu). This mixture (50 μl per well for 384-well plates, 200 μl per well for 96-well plates) was added to agonist in the assay plates (Multidrop 384, LabSystems). After incubation at 30°C. for 24 hours, fluorescence resulting from degradation of FDGlu to fluorescein due to exoglucanase, an endogenous yeast enzyme produced during agonist-

US 7,635,701 B2

23

stimulated cell growth, was determined using a Spectrofluor microtitre plate reader (Tecan; excitation wavelength: 485 nm, emission wavelength: 535 nm) Fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter fit to generate a concentration effect value Efficacy (E_{Max}) was calculated from the equation

$$E_{max} = \frac{Max_{[compound X]} - Min_{[compound X]} \cdot Max_{[HU210]}}{Min_{[HU210]} \times 100\%}$$

where $Max_{[compound X]}$ and $Min_{[compound X]}$ are the fitted maximum and minimum respectively from the concentration effect curve for compound X, and $Max_{[HU210]}$ and $Min_{[HU210]}$ are the fitted maximum and minimum respectively from the concentration effect curve for (6aR,10aR)-3-(1,1'-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol (HU210; available from Tocris). Equieffective molar ratio (EMR) values were calculated from the equation

$$EMR = EC_{50 [compound X]} / EC_{50 [HU210]}$$

Where $EC_{50 [compound X]}$ is the EC_{50} of compound X and $EC_{50 [HU210]}$ is the EC_{50} of HU210

Compounds of the Examples tested according to this method had EC_{50} values >2000 nM and/or efficacy values of <50% at the cloned human cannabinoid CB1 receptor.

Determination of Cannabinoid CB2 Receptor Agonist Activity

The cannabinoid CB2 receptor agonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

Yeast (*Saccharomyces cerevisiae*) cells expressing the human cannabinoid CB2 receptor were generated by integration of an expression cassette into the *ura3* chromosomal locus of yeast strain MMY23. This cassette consisted of DNA sequence encoding the human CB2 receptor flanked by the yeast GPD promoter to the 5' end of CB2 and a yeast transcriptional terminator sequence to the 3' end of CB2. MMY23 expresses a yeast/mammalian chimeric G-protein alpha subunit in which the C-terminal 5 amino acids of Gpa1 are replaced with the C-terminal 5 amino acids of human Gai3 (as described in Brown et al. (2000). Yeast 16:11-22) Cells were grown at 30° C. in liquid Synthetic Complete (SC) yeast media (Guthrie and Fink (1991). Methods in Enzymology, Vol. 194) lacking uracil, tryptophan, adenine and leucine to late logarithmic phase (approximately 6 OD₆₀₀ ml).

Agonists were prepared as 10 mM stocks in DMSO. EC_{50} values (the concentration required to produce 50% maximal response) were estimated using dilutions of between 3- and 5-fold (Biomek:FX, Beckman) into DMSO. Agonist solutions in DMSO (1% final assay volume) were transferred into black, clear bottom, microtitre plates from NUNC (96- or 384-well). Cells were suspended at a density of 0.2 OD₆₀₀/ml in SC media lacking histidine, uracil, tryptophan, adenine and leucine and supplemented with 10 mM 3-aminotriazole, 0.1M sodium phosphate pH 7.0, and 20M fluorescein di-β-D-glucopyranoside (FDGlu). This mixture (50 ul per well for 384-well plates, 200 ul per well for 96-well plates) was added to agonist in the assay plates (Multidrop 384, Labsystems). After incubation at 30° C. for 24 hours, fluorescence resulting from degradation of FDGlu to fluorescein due to exoglucanase, an endogenous yeast enzyme produced during agonist-stimulated cell growth, was determined using a Spectrofluor microtitre plate reader Tecan; excitation wavelength: 485 nm; emission wavelength: 535 nm). Fluorescence was plotted against compound concentration and iteratively curve fitted

24

using a four parameter fit to generate a concentration effect value. Efficacy (E_{Max}) was calculated from the equation

$$E_{max} = \frac{Max_{[compound X]} - Min_{[compound X]} \cdot Max_{[HU210]}}{Min_{[HU210]} \times 100\%}$$

where $Max_{[compound X]}$ and $Min_{[compound X]}$ are the fitted maximum and minimum respectively from the concentration effect curve for compound X, and $Max_{[HU210]}$ and $Min_{[HU210]}$ are the fitted maximum and minimum respectively from the concentration effect curve for (6aR,10aR)-3-(1,1'-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol (HU210; available from Tocris). Equieffective molar ratio (EMR) values were calculated from the equation

$$EMR = EC_{50 [compound X]} / EC_{50 [HU210]}$$

Where $EC_{50 [compound X]}$ is the EC_{50} of compound X and $EC_{50 [HU210]}$ is the EC_{50} of HU210.

Compounds of Examples 1 to 23, 31 to 56, 68, 163-256 tested according to this method had EC_{50} values 20 to 300 nM and efficacy values of >50% at the cloned human cannabinoid CB2 receptor

Compounds of Examples 24 to 30 and 73-113, and 257-259 tested according to this method had EC_{50} values 300 to 1000 nM or efficacy values of >50% at the cloned human cannabinoid CB2 receptor.

Compounds of Examples 57-67, 69-72, 114-162, and 260-265 tested according to this method had EC_{50} values >1000 nM or efficacy values of <50% at the cloned human cannabinoid CB2 receptor

The following examples are illustrative, but not limiting of the embodiments of the present invention.

All NMR experimental data was recorded at 400 MHz.

Conditions, Hardware, and Software used for Mass-directed Autopurification

Hardware

Waters 600 gradient pump, Waters 2700 Sample Manager, Waters Reagent Manager, Micromass ZMD mass spectrometer, Gilson 202—fraction collector, Gilson Aspec—waste collector.

Software

Micromass Masslynx version 3.5

Column

The column used is typically a Supelco ABZ+ column whose dimensions are 10 mm internal diameter by 100 mm in length. The stationary phase particle size is 5 μm.

Solvents

A. Aqueous solvent=Water+0.1% Formic Acid
B. Organic solvent=MeCN: Water 95:5+0.05% Formic Acid
Make up solvent=MeOH: Water 80:20+50 mMol Ammonium Acetate

Needle rinse solvent=MeOH: Water: DMSO 80:10:10

Methods

Five methods are used depending on the analytical retention time of the compound of interest. They all have a flow rate of 20 ml/min and a 15-minute runtime, which comprises of a 10-minute gradient followed by a 5-minute column flush and re-equilibration step

Method 1 MDP 1 5-2.2=0-30% B

Method 2 MDP 2.0-2.8=5-30% B

Method 3 MDP 2.5-3.0=15-55% B

Method 4 MDP 2.8-4.0=30-80% B

Method 5 MDP 3.8-5.5=50-90% B

US 7,635,701 B2

25

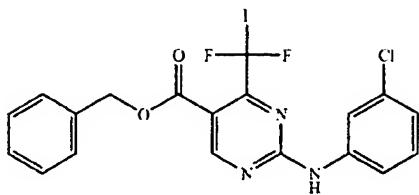
REFERENCE EXAMPLE 1

2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid benzylamide

(a). To a solution of benzyl 2-chloro-4-trifluoromethylpyrimidine-5-carboxylate (0.50 g, ex Maybridge) in 1,4-dioxan (5 ml) was added 3-chloroaniline (0.85 ml) and the solution stirred at room temperature for 15 h. 1,4-Dioxan was removed under reduced pressure and ethyl acetate (15 ml) added. The solution was washed sequentially with 2N hydrochloric acid (10 ml) and water (3x10 ml), dried (MgSO₄), evaporated and triturated with hexane to afford benzyl 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylate (524 mg).

NMR (DMSO-d₆) δ 5.35 (2H, s), 7.14 (1H, d), 7.35-7.45 (6H, m), 7.68 (1H, m), 7.98 (1H, s), 9.13 (1H, s), 10.95 (1H, s).

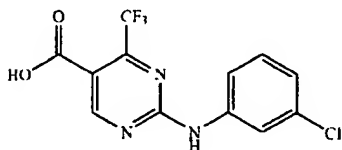
LC/MS, t=3.70 min. [MH⁺] 408 and 410.



(b) To a solution of benzyl 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylate (0.50 g) in ethanol (15 ml) was added a solution of potassium hydroxide (205 mg) in ethanol (10 ml) and the solution stirred at reflux for 15 h. Ethanol was removed under reduced pressure and water (15 ml) added. The solution was washed with ether and concentrated hydrochloric acid added to adjust the acidity to pH 1. The precipitated solid was filtered, washed with water and dried in vacuo at 50° C to afford 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (366 mg).

NMR (DMSO-d₆) δ 7.49 (1H, d), 7.71 (1H, t), 7.98 (1H, d), 8.33 (1H, s), 9.42 (1H, s), 11.15 (1H, s), 14.0 (1H, br s).

LC/MS, t=3.44 min. [MH⁺] 318 and 320.

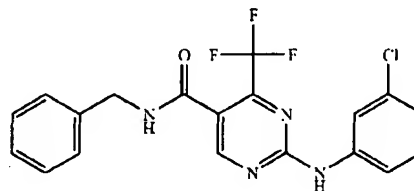


(c). To a solution of 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) in dimethylformamide (2 ml) was added successively N-ethylmorpholine (42 μl), benzylamine (15 μl), 1-hydroxybenzotriazole hydrate (23 mg) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (25 mg). The solution was stirred for 3 h and allowed to stand overnight. Dimethylformamide was removed under reduced pressure and ethyl acetate (5 ml) added. The solution was washed sequentially with 5% sodium bicarbonate solution (2.5 ml), water (2.5 ml), 5% citric acid solution (2.5 ml) and brine (2x2.5 ml), dried (MgSO₄) and evaporated to afford the title compound (45 mg).

26

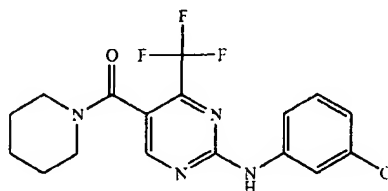
NMR (DMSO-d₆) δ 4.47 (2H, d), 7.10 (1H, d), 7.25 (1H, m), 7.36 (5H, m), 7.69 (1H, d), 7.98 (1H, s), 8.89 (1H, s), 9.12 (1H, t), 10.65 (1H, s).

LC/MS, t=3.23 min. [MH⁺] 407 and 409.



EXAMPLE 1

1-[2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-piperidin-1-ylmethanone



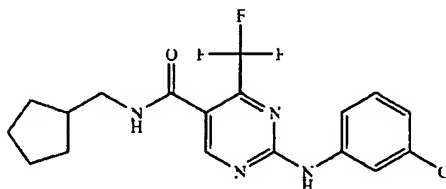
In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and piperidine (13 μl) afforded the title compound (38 mg).

NMR (DMSO-d₆) δ 1.3-1.65 (6H, m), 3.28 (2H, s), 3.6 (2H, br s), 7.10 (1H, d), 7.37 (1H, t), 7.68 (1H, d), 7.96 (1H, s), 8.78 (1H, s), 10.55 (1H, s).

LC/MS, t=3.63 min. [MH⁺] 385 and 387.

EXAMPLE 2

2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclopentylmethanamide



In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (100 mg) and cyclopentylmethanamine hydrochloride (63 mg, prepared as described in Kelley et al., J. Med. Chem., 40, 3207, (1997)) afforded the title compound (80 mg).

NMR (DMSO-d₆) δ 1.20-1.26 (2H, m), 1.48-1.67 (4H, m), 1.67-1.73 (2H, m), 2.06-2.10 (1H, quintuplet), 3.15-3.18 (2H, t), 7.09 (1H, dt), 7.37 (1H, q), 7.67 (1H, d), 7.96 (1H, d), 8.60-8.63 (1H, t), 8.79 (1H, s), 10.60 (1H, s).

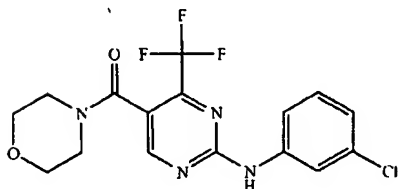
LC/MS, t=3.73 min. [MH⁺] 399.

US 7,635,701 B2

27

EXAMPLE 3

1-[2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholin-4-yl-methanone

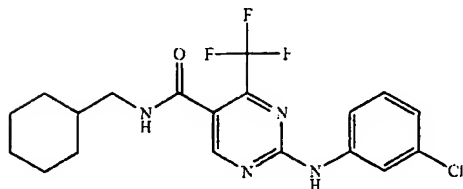


In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and morpholine (11.5 μ l) afforded the title compound (43 mg).

NMR (DMSO- d_6) δ 3.4-3.75 (8H, m), 7.10 (1H, d), 7.38 (1H, t), 7.68 (1H, d), 7.98 (1H, s), 8.80 (1H, s), 10.60 (1H, s)
LC/MS, t_r =3.29 min. [MH⁺] 387 and 389.

EXAMPLE 4

2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethylamide



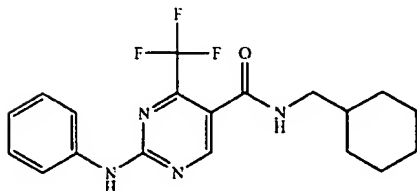
In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and cyclohexanemethylamine (15 mg) afforded the title compound (27 mg).

NMR (DMSO- d_6) δ 0.85-1.0 (2H, m), 1.1-1.3 (3H, m), 1.5 (1H, m), 1.55-1.8 (5H, m), 3.06 (2H, t), 7.09 (1H, d), 7.37 (1H, t), 7.68 (1H, d), 7.97 (1H, s), 8.58 (1H, t), 8.79 (1H, s), 10.6 (1H, s).

LC/MS, t_r =3.87 min. [MH⁺] 413 and 415.

EXAMPLE 5

2-Phenylamino-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexyl-1-methyl-amide



28

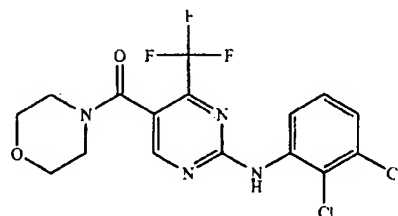
In a manner similar to Reference Example 1(c) 2-phenylamino-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and cyclohexanemethylamine (15 mg) afforded the title compound (33 mg).

NMR (DMSO- d_6) δ 0.85-1.0 (2H, m), 1.05-1.3 (3H, m), 1.5 (1H, m), 1.55-1.8 (5H, m), 3.08 (2H, t), 7.06 (1H, d), 7.35 (2H, t), 7.76 (2H, d), 8.56 (1H, t), 8.74 (1H, s), 10.4 (1H, s).

LC/MS, t_r =3.66 min. [MH⁺] 379

EXAMPLE 6

1-[2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholin-4-yl-methanone



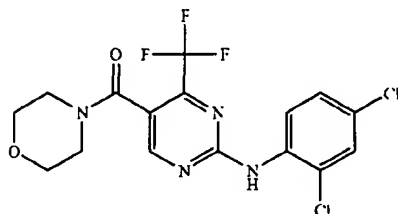
In a manner similar to Reference Example 1(c) 2-(2,3-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (24 mg) and morpholine (10 μ l) afforded the title compound (17 mg).

NMR (DMSO- d_6) δ 3.4-3.8 (8H, m), 7.40 (1H, t), 7.54 (1H, d), 7.60 (1H, d), 8.78 (1H, s), 10.15 (1H, s).

LC/MS, t_r =3.32 min. [MH⁺] 421 and 423.

EXAMPLE 7

1-[2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholin-4-yl-methanone



In a manner similar to Reference Example 1(c) 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (30 mg) and morpholine (10 μ l) afforded the title compound (31 mg).

NMR (DMSO- d_6) δ 3.3-3.8 (8H, m), 7.52 (1H, d of d), 7.68 (1H, d), 7.76 (1H, d), 8.73 (1H, s), 10.05 (1H, s).

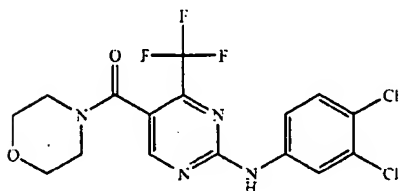
LC/MS, t_r =3.37 min. [MH⁺] 421 and 423.

US 7,635,701 B2

29

EXAMPLE 8

1-[2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholin-4-yl-methanone



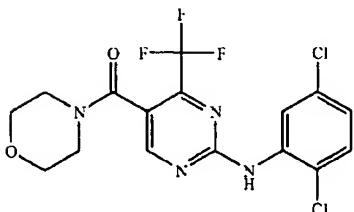
In a manner similar to Reference Example 1(c) 2-(3,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (30 mg) and morpholine (10 μ l) afforded the title compound (36 mg).

NMR (DMSO- d_6) δ 3.35-3.8 (8H, m), 7.67 (1H, d), 7.76 (1H, d of d), 8.22 (1H, s), 8.90 (1H, s), 10.80 (1H, s).

LC/MS, t_r 3.45 min, $[MH^+]$ 421 and 423.

EXAMPLE 9

1-[2-(2,5-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholin-4-yl-methanone



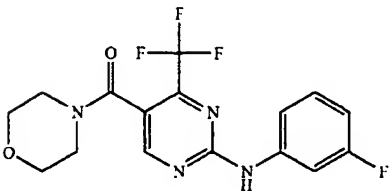
In a manner similar to Reference Example 1(c) 2-(2,5-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and morpholine (14.5 μ l) afforded the title compound (27 mg).

NMR (DMSO- d_6) δ 3.4-3.75 (8H, m), 7.32 (1H, d of d), 7.66 (1H, d), 7.78 (1H, d), 8.71 (1H, s), 10.05 (1H, s).

LC/MS, t_r 3.31 min, $[MH^+]$ 421 and 423.

EXAMPLE 10

1-[2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholin-4-yl-methanone



30

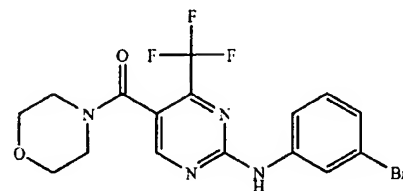
In a manner similar to Reference Example 1(c) 2-(3-fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and morpholine (12 μ l) afforded the title compound (31 mg).

NMR (DMSO- d_6) δ 3.4-3.8 (8H, m), 6.85 (1H, t of d), 7.37 (1H, q), 7.52 (1H, d), 7.77 (1H, d of t), 8.80 (1H, s), 10.65 (1H, s).

LC/MS, t_r 3.06 min, $[MH^+]$ 371.

EXAMPLE 11

1-[2-(3-Bromophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholin-4-yl-methanone



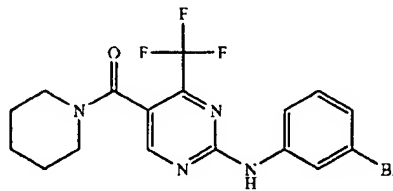
In a manner similar to Reference Example 1(c) 2-(3-bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and morpholine (10 μ l) afforded the title compound (31 mg).

NMR (DMSO- d_6) δ 3.4-3.8 (8H, m), 7.22 (1H, d), 7.30 (1H, t), 7.71 (1H, d), 8.11 (1H, s), 8.81 (1H, s), 10.60 (1H, s).

LC/MS, t_r 3.25 min, $[MH^+]$ 431 and 433.

EXAMPLE 12

1-[2-(3-Bromophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-piperidin-4-yl-methanone



In a manner similar to Reference Example 1(c) 2-(3-bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and piperidine (12 μ l) afforded the title compound (31 mg).

NMR (DMSO- d_6) δ 1.3-1.7 (6H, m), 3.26 (2H, s), 3.60 (2H, br s), 7.21 (1H, d), 7.30 (1H, t), 7.70 (1H, d), 8.11 (1H, s), 8.78 (1H, s), 10.55 (1H, s).

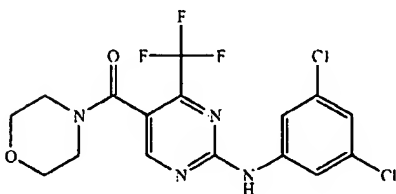
LC/MS, t_r 3.57 min, $[MH^+]$ 429 and 431.

US 7,635,701 B2

31

EXAMPLE 13

1-[2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-morpholin-4-yl-methanone



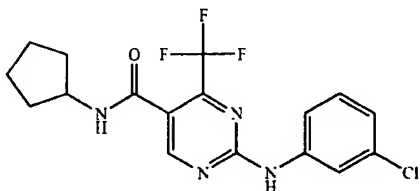
In a manner similar to Reference Example 1(c) 2-(3,5-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg) and morpholine (14.5 μ l) afforded the title compound (42 mg).

NMR (DMSO-d₆) δ 3.4-3.75 (8H, m), 7.35 (1H, s), 7.89 (2H, s), 8.87 (1H, s), 10.80 (1H, s).

LC/MS, t_r =3.52 min, [M+]⁺ 421 and 423.

EXAMPLE 14

2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclopentylamide



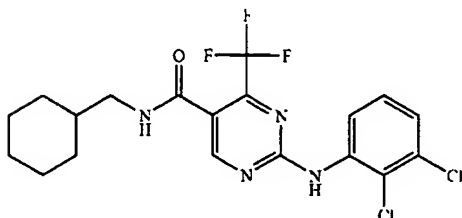
In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and cyclopentylamine (13 μ l) afforded the title compound (34 mg).

NMR (DMSO-d₆) δ 1.5 (4H, m), 1.65 (2H, m), 1.85 (2H, m), 4.15 (1H, m), 7.09 (1H, d), 7.36 (1H, t), 7.67 (1H, d), 7.97 (1H, s), 8.55 (1H, d), 8.79 (1H, s), 10.60 (1H, s).

LC/MS, t_r =3.55 min, [M+]⁺ 385 and 387.

EXAMPLE 15

2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide



32

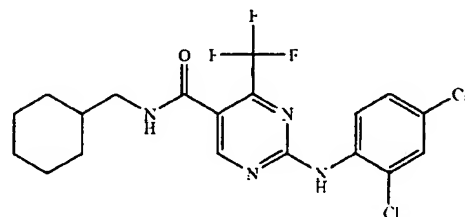
In a manner similar to Reference Example 1(c) 2-(2,3-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg) and cyclohexanemethylamine (16 μ l) afforded the title compound (30 mg).

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.3 (3H, m), 1.45 (1H, m), 1.55-1.8 (5H, m), 3.05 (2H, t), 7.40 (1H, t), 7.55 (2H, d), 8.53 (1H, t), 8.65 (1H, s), 10.15 (1H, s).

LC/MS, t_r =3.84 min, [M+]⁺ 447 and 449.

EXAMPLE 16

2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide



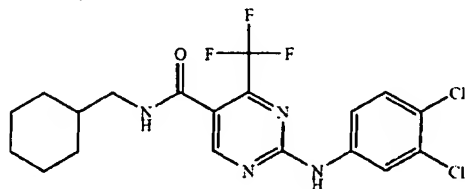
In a manner similar to Reference Example 1(c) 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg) and cyclohexanemethylamine (16 μ l) afforded the title compound (14 mg).

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.3 (3H, m), 1.45 (1H, m), 1.55-1.75 (5H, m), 3.05 (2H, t), 7.46 (1H, d), 7.57 (1H, d), 7.72 (1H, s), 8.53 (1H, t), 8.64 (1H, s), 10.00 (1H, s).

LC/MS, t_r =3.90 min, [M+]⁺ 447 and 449.

EXAMPLE 17

2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide



In a manner similar to Reference Example 1(c) 2-(3,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg) and cyclohexanemethylamine (16 μ l) afforded the title compound (31 mg).

NMR (DMSO-d₆) δ 0.8-1.0 (2H, m), 1.1-1.3 (3H, m), 1.5 (1H, m), 1.55-1.8 (5H, m), 3.06 (2H, t), 7.62 (1H, d), 7.69 (1H, d), 8.18 (1H, s), 8.59 (1H, t), 8.82 (1H, s), 10.70 (1H, s).

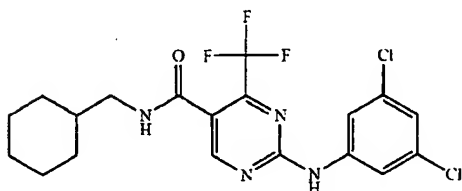
LC/MS, t_r =4.01 min, [M+]⁺ 447 and 449.

US 7,635,701 B2

33

EXAMPLE 18

2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide



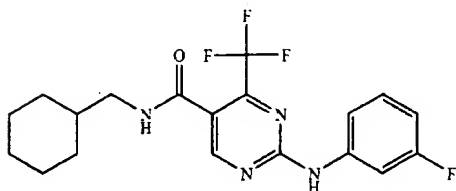
In a manner similar to Reference Example 1(c) 2-(3,5-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg) and cyclohexanemethylamine (16 μ l) afforded the title compound (30 mg)

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.3 (3H, m), 1.5 (1H, m), 1.55-1.8 (5H, m), 3.07 (2H, t), 7.26 (1H, s), 7.89 (2H, s), 8.58 (1H, t), 8.86 (1H, s), 10.80 (1H, s).

LC/MS, t=4.08 min [MH⁺] 447 and 449.

EXAMPLE 19

2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide



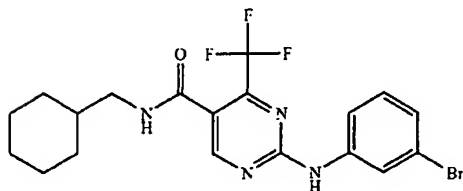
In a manner similar to Reference Example 1(c) 2-(3-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg) and cyclohexanemethylamine (18 μ l) afforded the title compound (38 mg).

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.3 (3H, m), 1.5 (1H, m), 1.55-1.8 (5H, m), 3.09 (2H, t), 6.87 (1H, t of d), 7.39 (1H, q), 7.53 (1H, d), 7.78 (1H, d of t), 8.59 (1H, t), 8.80 (1H, s), 10.60 (1H, s).

LC/MS, t=3.68 min, [MH⁺] 397.

EXAMPLE 20

2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide



In a manner similar to Reference Example 1(c) 2-(3-bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg) and cyclohexanemethylamine (15 μ l) afforded the title compound (36 mg).

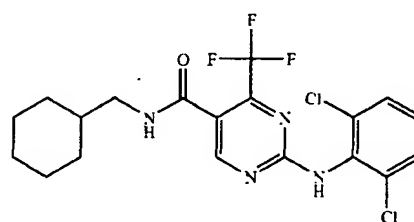
34

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.3 (3H, m), 1.5 (1H, m), 1.55-1.8 (5H, m), 3.08 (2H, t), 7.23 (1H, d), 7.31 (1H, t), 7.71 (1H, d), 8.10 (1H, s), 8.57 (1H, t), 8.80 (1H, s), 10.60 (1H, s).

LC/MS, t=3.85 min, [MH⁺] 457 and 459

EXAMPLE 21

2-(2,6-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethyl-amide



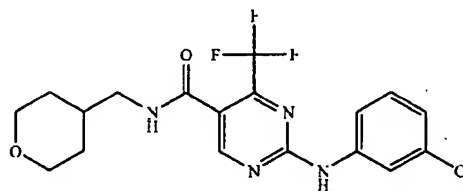
In a manner similar to Reference Example 1(c) 2-(2,6-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (33 mg) and cyclohexanemethylamine (15 μ l) afforded the title compound (9 mg).

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.05-1.25 (3H, m), 1.46 (1H, m), 1.55-1.8 (5H, m), 3.04 (2H, t), 7.39 (1H, t), 7.59 (2H, d), 8.56 (2H, m), 10.10 (1H, s).

LC/MS, t=3.84 min, [MH⁺] 447 and 449.

EXAMPLE 22

2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (30 mg) and 4-aminomethyltetrahydropyran (13 mg) afforded the title compound (25 mg).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.62 (2H, d), 1.74 (1H, m), 3.13 (2H, t), 3.27 (2H, t), 3.86 (2H, d), 7.10 (1H, d), 7.37 (1H, t), 7.66 (1H, d), 7.97 (1H, s), 8.63 (1H, t), 8.82 (1H, s), 10.60 (1H, s).

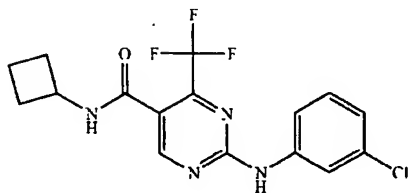
LC/MS, t=3.22 min, [MH⁺] 415 and 417.

US 7,635,701 B2

35

EXAMPLE 23

2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclobutyl-amide



In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg) and cyclobutylamine (10 μ l) afforded the title compound (28 mg).

36

NMR (DMSO- d_6) δ 1.6-1.75 (2H, m), 1.9-2.05 (2H, m), 2.2-2.3 (2H, m), 4.32 (1H, m), 7.10 (1H, d), 7.37 (1H, t), 7.67 (1H, d), 7.96 (1H, s), 8.82 (2H, s), 10.60 (1H, s).

LC/MS, t_r 3.45 min, $[MH^+]$ 371 and 373.

EXAMPLES 24 TO 30

Table 1) gives examples 24 to 30, column 1 gives the precursors that were reacted with methyl 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylate in a manner similar to that in Reference example 1(a). In a manner similar to that in Reference example 1(h), the carboxylic acid of the resultant ester was prepared. Finally, in a manner similar to that of Reference example 1(c), the resultant acid product was reacted with the precursor of column 2 to provide the final product of column 3.

TABLE 1

Ex 1	2	3 - Product	Structure	LC/MS 1 Retention time (min) 2 MH^+ 3 Formula
24 Aniline	Piperidine	1-(2-Phenylamino-4-trifluoromethyl-pyrimidin-5-yl)-1-piperidin-1-yl-methanone		3.38 351 $C_{17}H_{17}F_3N_4O$
25 Aniline	Morpholine	1-Morpholin-4-yl-1-(2-phenylamino-4-trifluoromethyl-pyrimidin-5-yl)-methanone		3.04 353 $C_{16}H_{15}F_3N_4O_2$
26 3-Chloroaniline	Amineacetonitrile	2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyanomethyl-amide		3.27 356 $C_{14}H_9^{35}ClF_3N_5O$
27 3-Chloroaniline	3,3-Dimethylbutyl amine	2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (3,3-dimethyl-butyl)-amide		3.80 411 $C_{18}H_{29}^{35}ClF_3N_5O$

US 7,635,701 B2

37

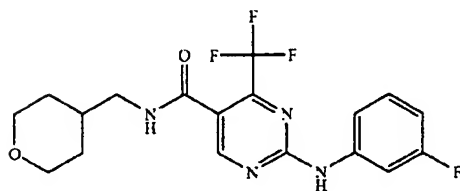
38

TABLE 1-continued

Ex 1	2	3 - Product	Structure	LC MS 1 Retention time (min) 2 MH ⁺ 3 Formula
28	3-Chloroaniline	Neopentylamine	2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (2,2-dimethyl-propyl)-amide	3.69 387 C ₁₇ H ₁₉ ³⁵ Cl F ₃ N ₄ O
29	3-Fluoroaniline	Cyclobutylamine	2-(3-Fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylamide	3.29 355 C ₁₆ H ₁₄ F ₃ N ₄ O
30	3,4-Dichloroaniline	Cyclobutylamine	2-(3,4-Dichloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylamide	3.66 405 C ₁₆ H ₁₃ ³⁵ Cl ₂ F ₃ N ₄ O

EXAMPLE 31

2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl) amide



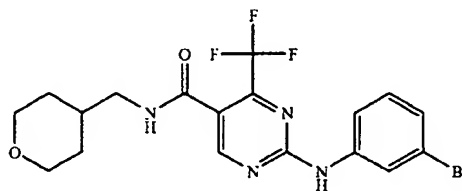
In a manner similar to Reference Example 1(c) 2-(3-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg) and 4-aminomethyltetrahydropyran (16 mg) afforded the title compound (38 mg)

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.63 (2H, d), 1.75 (1H, m), 3.15 (2H, t), 3.29 (2H, t), 3.86 (2H, d), 6.88 (1H, td), 7.38 (1H, q), 7.51 (1H, d), 7.76 (1H, dt), 8.64 (1H, t), 8.82 (1H, s), 10.60 (1H, s).

LC/MS, t=3.08 min, [MH⁺] 399.

EXAMPLE 32

2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl) amide



In a manner similar to Reference Example 1(c) 2-(3-bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg) and 4-aminomethyltetrahydropyran (13.5 mg) afforded the title compound (36 mg).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.62 (2H, d), 1.74 (1H, m), 3.13 (2H, t), 3.27 (2H, t), 3.86 (2H, d), 7.23 (1H, d), 7.31 (1H, t), 7.71 (1H, d), 8.11 (1H, s), 8.63 (1H, t), 8.82 (1H, s), 10.60 (1H, s).

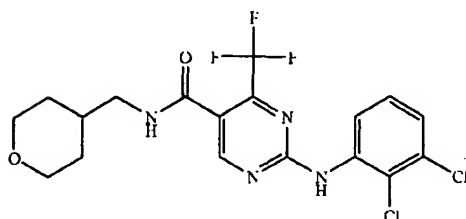
LC/MS, t=3.26 min, [MH⁺] 459 and 461.

US 7,635,701 B2

39

EXAMPLE 33

2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)amide



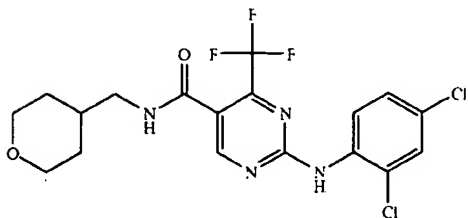
In a manner similar to Reference Example 1(c) 2-(2,3-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (30 mg) and 4-aminomethyltetrahydropyran (12 mg) afforded the title compound (25 mg).

NMR (DMSO-d₆) δ 1.1-1.25 (2H, m), 1.60 (2H, d), 1.72 (1H, m), 3.11 (2H, t), 3.26 (2H, t), 3.85 (2H, d), 7.40 (1H, t), 7.55 (2H, d), 8.60 (1H, t), 8.66 (1H, s), 10.10 (1H, s).

LC/MS, t=3.29 min, [MH⁺] 449 and 451.

EXAMPLE 34

2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)amide



In a manner similar to Reference Example 1(c) 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (30 mg) and 4-aminomethyltetrahydropyran (12 mg) afforded the title compound (34 mg).

NMR (DMSO-d₆) δ 1.1-1.25 (2H, m), 1.59 (2H, d), 1.72 (1H, m), 3.11 (2H, t), 3.26 (2H, t), 3.85 (2H, d), 7.47 (1H, dd), 7.57 (1H, d), 7.72 (1H, s), 8.60 (1H, t), 8.65 (1H, s), 10.05 (1H, s).

LC/MS, t=3.33 min, [MH⁺] 449 and 451.

Additional Synthesis of Example 34

2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide

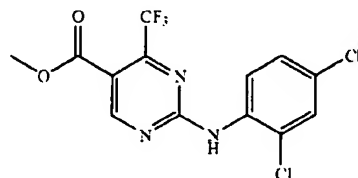
(a). To a solution of methyl 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylate (0.50 g, ex Maybridge) in 1,4-dioxan (5 ml) was added 2,4-dichloroaniline (1.7 g) and the solution stirred under reflux for 7 h. 1,4-Dioxan was removed under reduced pressure and ethyl acetate (15 ml) added. The

40

solution was washed sequentially with 2N hydrochloric acid (10 ml) and water (3×10 ml), dried (MgSO₄), evaporated and triturated with hexane to afford methyl 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylate (358 mg).

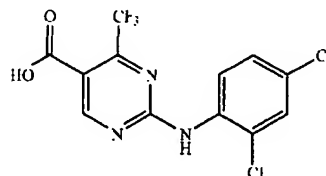
NMR (CDCl₃) δ 3.95 (3H, s), 7.30 (1H, dd), 7.45 (1H, d), 8.00 (1H, s), 8.5 (1H, d), 9.05 (1H, s).

LC/MS, t=3.74 min, [MH⁺]366.



(b). To a solution of methyl 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylate (0.358 g) in ethanol (8 ml) was added a solution of potassium hydroxide (190 mg) in ethanol (8 ml) and the solution stirred at reflux for 24 h. Ethanol was removed under reduced pressure and water (15 ml) added. The solution was washed with ether and concentrated hydrochloric acid was added to adjust the acidity to pH 1. The precipitated solid was filtered, washed with water and dried in vacuo at 50° C. to afford 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (262 mg).

NMR (DMSO-d₆) δ 7.48 (1H, dd), 7.60 (1H, d), 7.73 (1H, d), 8.95 (1H, s), 10.3 (1H, s), 13.6 (1H, s).

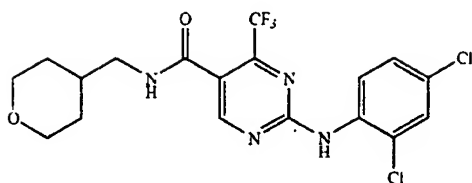


(c). To a solution of 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (30 mg) in dimethylformamide (2 ml) was added successively N-ethylmorpholine (33 μl), 4-aminomethyltetrahydropyran (12 mg), 1-hydroxybenzotriazole hydrate (18 mg) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (20 mg). The solution was stirred for 3 h and allowed to stand overnight. Dimethylformamide was removed under reduced pressure and ethyl acetate (5 ml) added. The solution was washed sequentially with 5% sodium bicarbonate solution (2.5 ml), water (2.5 ml), 5% citric acid solution (2.5 ml) and brine (2×2.5 ml), dried (MgSO₄) and evaporated to afford the title compound (34 mg) NMR (DMSO-d₆) δ 1.20 (2H, m), 1.58 (2H, d), 1.70 (1H, m), 3.10 (2H, t), 3.23 (2H, t), 3.84 (2H, dd), 7.46 (1H, dd), 7.57 (1H, d), 7.71 (1H, d), 8.59 (1H, t), 8.63 (1H, s), 10.00 (1H, s).

LC/MS, t=3.33 min, [MH⁺] 449.

US 7,635,701 B2

41



Additional Synthesis of Example 34

2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide

(a). To a solution of methyl 2-chloro-4-trifluoromethylpyrimidine-5-carboxylate (70 g, ex Maybridge 22 g, ex Fluorochem 48 g) in 1,4-dioxan (100 n-1) was added 2,4-dichloroaniline (142 g) and the solution stirred under reflux for 10.5 h. 1,4-Dioxan was partially removed (approx 50 ml) under reduced pressure and 2N HCl (800 ml) added. The mixture was stirred with overhead stirring for 3 h and the resulting solid filtered onto a sinter. The solid was washed with 2N HCl (2x300 ml) and water (4x400 ml) then dried over sodium hydroxide in vacuo at 50° C. to afford methyl 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylate. The solid contained approximately 5% 2,4-dichloroaniline

NMR (DMSO-d₆) δ 3.84 (3H, s), 7.47 (1H, dd), 7.49 (1H, d), 7.74 (1H, d), 8.96 (1H, s), 10.45 (1H, s).

LC/MS. t_r 3.66 min, [MH⁺] 366.

(b). To a solution of methyl 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylate (107 g) in methanol (700 ml) was added a solution of potassium hydroxide (50 g) in methanol (700 ml) and the solution stirred at reflux for 24 h. Methanol was removed under reduced pressure and water (800 ml) added. The solution was washed with ether (3x400 ml, which removed the remaining 2,4-dichloroaniline) and concentrated hydrochloric acid added to adjust the acidity to pH 1. The precipitated solid was filtered, washed with 2N HCl and water until the pH of the filtrate was neutral. The solid was dried in vacuo at 50° C. to afford 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (86.9 g)

NMR (DMSO-d₆) δ 7.48 (1H, dd), 7.60 (1H, d), 7.73 (1H, d), 8.95 (1H, s), 10.3 (1H, s), 13.6 (1H, s).

LC/MS. t_r 4.35 min, [MH⁺] 352

(c). To a solution of 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (86 g) in dimethylformamide (800 ml) was added successively N-ethylmorpholine (93 ml), 4-aminomethyltetrahydropyran (29.5 g), 1-hydroxybenzotriazole hydrate (51.5 g) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (56.2 g). The solution was stirred for 24 h. Dimethylformamide was partially removed (approx 650 ml) under reduced pressure and 5% sodium bicarbonate solution added (3x500 ml, added portionwise to control the release of carbon dioxide). The mixture was stirred with overhead stirring for 3 h and the resulting solid filtered onto a sinter. The solid was washed with 5% sodium bicarbonate (4x400 ml) and water (3x400 ml) then dried over sodium hydroxide in vacuo at 50° C. to afford the title compound (109.1 g)

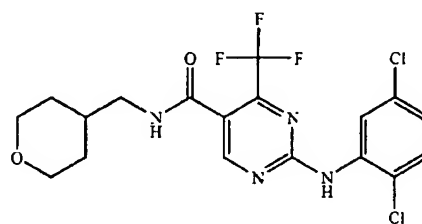
42

NMR (DMSO-d₆) δ 1.20 (2H, m), 1.58 (2H, d), 1.70 (1H, m), 3.10 (2H, t), 3.23 (2H, t), 3.84 (2H, dd), 7.46 (1H, dd), 7.57 (1H, d), 7.71 (1H, d), 8.59 (1H, t), 8.63 (1H, s), 10.00 (1H, s)

LC/MS. t_r 3.41 min, [MH⁺] 449.

EXAMPLE 35

2-(2,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



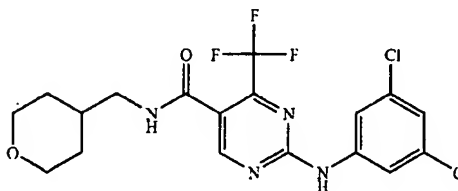
In a manner similar to Reference Example 1(c) 2-(2,5-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (50 mg) and 4-aminomethyltetrahydropyran (25 mg) afforded the title compound (63 mg).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.60 (2H, d), 1.72 (1H, m), 3.12 (2H, t), 3.27 (2H, t), 3.85 (2H, d), 7.35 (1H, dd), 7.59 (1H, d), 7.73 (1H, s), 8.62 (1H, t), 8.70 (1H, s), 10.05 (1H, s).

LC/MS. t_r 3.30 min, [MH⁺] 449 and 451.

EXAMPLE 36

2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



In a manner similar to Reference Example 1(c) 2-(3,5-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (50 mg) and 4-aminomethyltetrahydropyran (25 mg) afforded the title compound (68 mg).

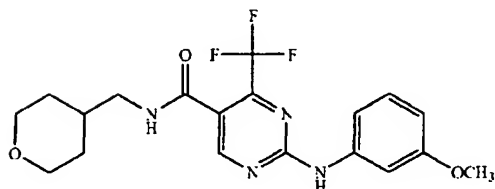
NMR (DMSO-d₆) δ 1.15-1.35 (2H, m), 1.62 (2H, d), 1.72 (1H, m), 3.14 (2H, t), 3.28 (2H, t), 3.86 (2H, d), 7.25 (1H, s), 7.88 (2H, s), 8.66 (1H, t), 8.88 (1H, s), 10.75 (1H, s).

US 7,635,701 B2

43

EXAMPLE 37

2-(3-Methoxyphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



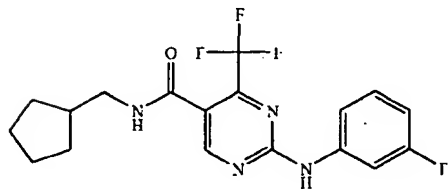
In a manner similar to Reference Example 1(c) 2-(3-methoxyphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (32 mg) and 4-aminomethyltetrahydropyran (14.5 mg) afforded the title compound (29 mg).

NMR (DMSO-d₆) δ 1.1-1.25 (2H, m), 1.61 (2H, d), 1.74 (1H, m), 3.13 (2H, t), 3.27 (2H, t), 3.74 (3H, s), 3.86 (2H, d), 6.63 (1H, d), 7.25 (2H, m), 7.53 (1H, s), 8.62 (1H, t), 8.76 (1H, s), 10.35 (1H, s).

LC/MS. t=2.97 min. [MH⁺] 411.

EXAMPLE 38

2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclopentylmethyl-amide



In a manner similar to Reference Example 1(c) 2-(3-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (30 mg) and cyclopentylmethylamine hydrochloride (17 mg, prepared as described in Kelley et al., J. Med. Chem., 40, 3207, (1997)) afforded the title compound (17 mg).

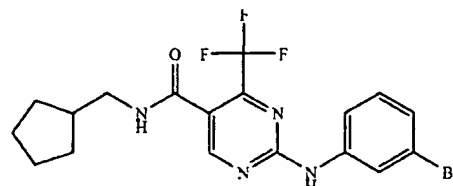
NMR (DMSO-d₆) δ 1.20-1.30 (2H, m), 1.45-1.68 (4H, m), 1.68-1.77 (2H, m), 2.1 (1H, quintuplet), 3.19 (2H, t), 6.89 (1H, dt), 7.40 (1H, q), 7.54 (1H, d), 7.78 (1H, d), 8.64 (1H, t), 8.80 (1H, s), 10.70 (1H, s).

LC/MS. t=3.53 min. [MH⁺] 383.

44

EXAMPLE 39

2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclopentylmethyl-amide



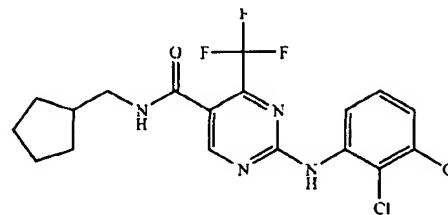
In a manner similar to Reference Example 1(c) 2-(3-bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36.5 mg) and cyclopentylmethylamine hydrochloride (17 mg) afforded the title compound (28 mg).

NMR (DMSO-d₆) δ 1.39-1.52 (2H, m), 1.69-1.90 (4H, m), 1.90-2.02 (2H, m), 2.34 (1H, quintuplet), 3.4 (2H, t), 7.48 (1H, d), 7.57 (1H, t), 7.95 (1H, d), 8.37 (1H, s), 8.86 (1H, t), 9.02 (1H, s), 10.80 (1H, s).

LC/MS. t=3.33 min. [MH⁺] 443 and 445.

EXAMPLE 40

2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclopentylmethyl-amide



In a manner similar to Reference Example 1(c) 2-(2,3-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (32 mg) and cyclopentylmethylamine hydrochloride (15 mg) afforded the title compound (30 mg).

NMR (DMSO-d₆) δ 1.15-1.30 (2H, m), 1.44-1.78 (4H, m), 2.10 (1H, quintuplet), 3.16 (2H, t), 7.41 (2H, t), 7.54 (1H, m), 8.58 (1H, br t), 8.78 (1H, s), 10.10 (1H, s).

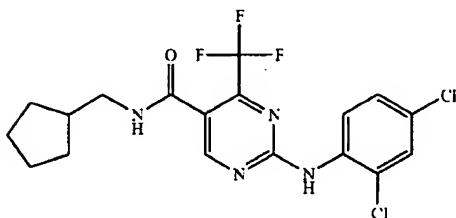
LC/MS. t=3.71 min. [MH⁺] 433 and 435.

US 7,635,701 B2

45

EXAMPLE 41

2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclopentylmethyl-amide



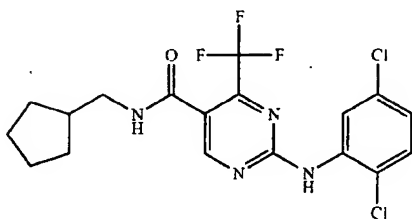
In a manner similar to Reference Example 1(c) 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (32 mg) and cyclopentylmethylamine hydrochloride (15 mg) afforded the title compound (27 mg).

NMR (DMSO-d₆) δ 1.2-1.3 (2H, m), 1.4-1.79 (6H, m), 2.10 (1H, quintuplet), 3.17 (2H, t), 7.50 (1H, d), 7.60 (1H, d), 7.75 (1H, d), 8.68 (1H, t), 8.78 (1H, s), 10.10 (1H, s).

LC/MS, t_r =3.76 min, [MH⁺] 433 and 435.

EXAMPLE 42

2-(2,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclopentylmethyl-amide



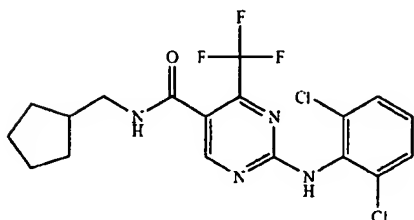
In a manner similar to Reference Example 1(c) 2-(2,5-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (32 mg) and cyclopentylmethylamine hydrochloride (15 mg) afforded the title compound (23 mg).

NMR (DMSO-d₆) δ 1.15-1.30 (2H, m), 1.45-1.79 (6H, m), 2.08 (1H, quintuplet), 3.18 (2H, t), 7.38 (1H, d), 7.62 (1H, d), 7.75 (1H, s), 8.61 (1H, br t), 8.71 (1H, s), 10.05 (1H, s).

LC/MS, t_r =3.76 min, [MH⁺] 433 and 435.

EXAMPLE 43

2-(2,6-Dichlorophenylamino)-trifluoromethylpyrimidine-5-carboxylic acid cyclopentylmethyl-amide



46

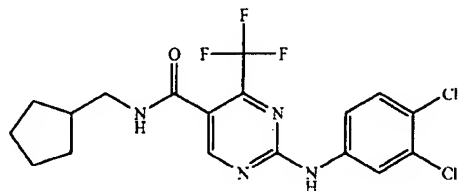
In a manner similar to Reference Example 1(c) 2-(2,6-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (32 mg) and cyclopentylmethylamine hydrochloride (15 mg) afforded the title compound (25 mg)

NMR (DMSO-d₆) δ 1.15-1.30 (2H, m), 1.45-1.78 (6H, m), 2.08 (1H, quintuplet), 3.15 (2H, t), 7.4 (1H, t), 7.6-7.68 (2H, m), 8.5-8.7 (2H, m), 10.20 (1H, s).

LC/MS, t_r =3.49 min, [MH⁺] 433 and 435.

EXAMPLE 44

2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclopentylethyl-amide



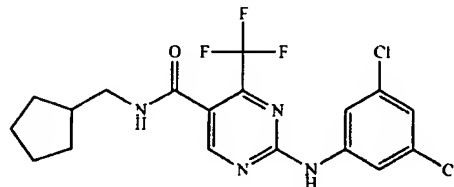
In a manner similar to Reference Example 1(c) 2-(3,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (32 mg) and cyclopentylmethylamine hydrochloride (15 mg) afforded the title compound (29 mg).

NMR (DMSO-d₆) δ 1.12-1.3 (2H, m), 1.44-1.8 (6H, m), 2.1 (1H, quintuplet), 3.17 (2H, t), 7.62 (1H, br d), 7.72 (1H, d), 8.18 (1H, d), 8.60-8.69 (1H, br t), 8.83 (1H, s), 10.80 (1H, s).

LC/MS, t_r =3.87 min, [MH⁺] 433 and 435.

EXAMPLE 45

2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclopentylmethyl-amide



In a manner similar to Reference Example 1(c) 2-(3,5-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (32 mg) and cyclopentylmethylamine hydrochloride (15 mg) afforded the title compound (27 mg).

NMR (DMSO-d₆) 1.14-1.34 (2H, m), 1.45-1.8 (6H, m), 2.10 (1H, quintuplet), 3.20 (2H, t), 7.28 (1H, s), 7.91 (2H, s), 8.6-8.7 (1H, br t), 8.9 (1H, s), 10.75 (1H, s).

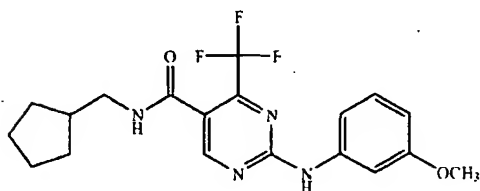
LC/MS, t_r =3.94 min, [MH⁺] 433 and 435.

US 7,635,701 B2

47

EXAMPLE 46

2-(3-Methoxyphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclopentylmethylamide



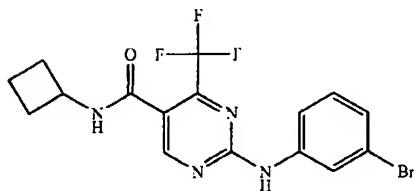
In a manner similar to Reference Example 1(c) 2-(3-methoxyphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and cyclopentylmethylamine hydrochloride (17 mg) afforded the title compound (21 mg)

NMR (DMSO-d₆) δ 1.25-1.38 (2H, m), 1.50-1.85 (6H, m), 2.15 (1H, quintuplet), 3.25 (2H, t), 3.85 (3H, s), 6.70 (1H, br d), 7.26-7.37 (2H, m), 7.60 (1H, m), 8.68 (1H, t), 8.80 (1H, s), 10.50 (1H, s)

LC/MS, t=3.46 min, [MH⁺] 395.

EXAMPLE 47

2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclobutylamide



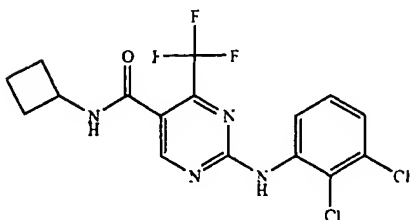
In a manner similar to Reference Example 1(c) 2-(3-bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (35 mg) and cyclobutylamine (10 μl) afforded the title compound (30 mg).

NMR (DMSO-d₆) δ 1.70 (2H, m), 1.97 (2H, m), 2.22 (2H, m), 4.32 (1H, m), 7.22-7.33 (2H, m), 7.70 (1H, d), 8.10 (1H, s), 8.81-8.83 (2H, m), 10.60 (1H, s).

LC/MS, t=3.47 min, [MH⁺] 415 and 417.

EXAMPLE 48

2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclobutylamide



48

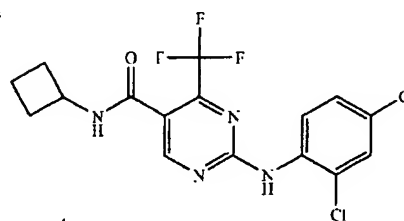
In a manner similar to Reference Example 1(c) 2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (25 mg) and cyclobutylamine (10 μl) afforded the title compound (20 mg).

NMR (DMSO-d₆) δ 1.70 (2H, m), 1.97 (2H, m), 2.22 (2H, m), 4.32 (1H, m), 7.38-7.56 (3H, m), 8.65 (1H, s), 8.80 (1H, d), 10.10 (1H, s).

LC/MS, t=3.48 min, [MH⁺] 405 and 407.

EXAMPLE 49

2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclobutylamide



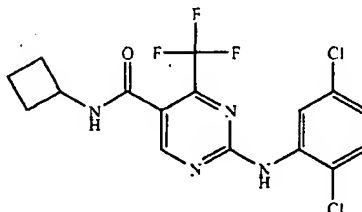
In a manner similar to Reference Example 1(c) 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (30 mg) and cyclobutylamine (10 μl) afforded the title compound (26 mg).

NMR (DMSO-d₆) δ 1.70 (2H, m), 1.97 (2H, m), 2.22 (2H, m), 4.32 (1H, m), 7.46-7.72 (3H, m), 8.64 (1H, s), 8.80 (1H, d), 10.00 (1H, s).

LC/MS, t=3.54 min, [MH⁺] 405 and 407.

EXAMPLE 50

2-(2,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclobutylamide



In a manner similar to Reference Example 1(c) 2-(2,5-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (50 mg) and cyclobutylamine (19 μl) afforded the title compound (56 mg).

NMR (DMSO-d₆) δ 1.70 (2H, m), 1.97 (2H, m), 2.22 (2H, m), 4.30 (1H, m), 7.33-7.73 (3H, m), 8.70 (1H, s), 8.80 (1H, d), 10.00 (1H, s).

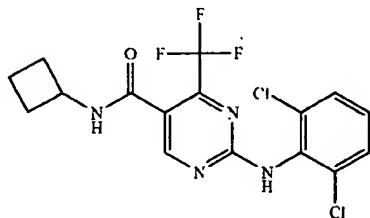
LC/MS, t=3.52 min, [MH⁺] 405 and 407.

US 7,635,701 B2

49

EXAMPLE 51

2-(2,6-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid N-cyclobutylamide



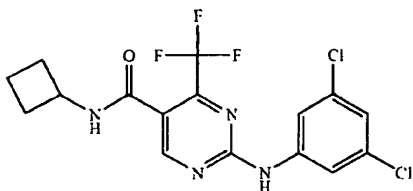
In a manner similar to Reference Example 1(c) 2-(2,6-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (30 mg) and cyclobutylamine (10 μ l) afforded the title compound (34 mg).

NMR (DMSO- d_6) δ 1.70 (2H, m), 1.97 (2H, m), 2.22 (2H, m), 4.30 (1H, m), 7.36-7.60 (3H, m), 8.59 (1H, s), 8.80 (1H, d), 10.15 (1H, s).

LC/MS. t_r 3.24 min. [MH⁺] 405 and 407.

EXAMPLE 52

2-(3,5-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclobutylamide



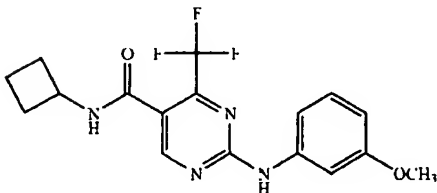
In a manner similar to Reference Example 1(c) 2-(3,5-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (50 mg) and cyclobutylamine (19 μ l) afforded the title compound (56 mg).

NMR (DMSO- d_6) δ 1.70 (2H, m), 1.97 (2H, m), 2.22 (2H, m), 4.32 (1H, m), 7.25-7.87 (3H, m), 8.85 (1H, d), 8.88 (1H, s), 10.80 (1H, s).

LC/MS. t_r 3.73 min. [MH⁺] 405 and 407.

EXAMPLE 53

2-(3-Methoxyphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclobutylamide



In a manner similar to Reference Example 1(c) 2-(3-methoxyphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (32 mg) and cyclobutylamine (10.5 μ l) afforded the title compound (27 mg).

50

NMR (DMSO- d_6) δ 1.70 (2H, m), 1.97 (2H, m), 2.22 (2H, m), 3.75 (3H, s), 4.32 (1H, m), 7.53-7.87 (4H, m), 8.76 (1H, s), 8.81 (1H, d), 10.40 (1H, s).

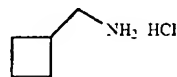
LC/MS. t_r 3.20 min. [MH⁺] 367.

EXAMPLE 54

2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclobutylmethylamide

(a) A solution of borane-tetrahydrofuran complex (1M in tetrahydrofuran, 120 ml) was added over 10 min to a solution of cyclobutane carbonitrile (8.1 g) [A Lancaster] in dry tetrahydrofuran (20 ml) under nitrogen at room temperature. The solution was refluxed overnight then cooled to 20°. Methanol (150 ml) was added dropwise over 15 mins keeping the temperature below 25°, then the mixture was cooled to 0° and dry hydrogen chloride was bubbled through for 30 min. The resulting mixture was refluxed for 90 min, evaporated and the residue re-evaporated twice from methanol. Ether (150 ml) was added and the resulting solid was filtered off. It was taken up in hot isopropanol (50 ml), filtered, and hot acetonitrile (30 ml) added. The mixture was cooled and the solid filtered off to give the C-cyclobutylmethylamine hydrochloride (5.7 g).

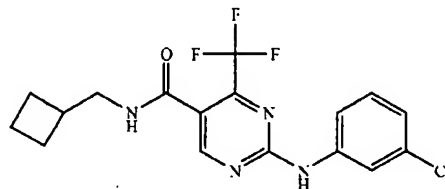
NMR (400 MHz, DMSO- d_6) δ 1.8 (4H, m), 2.0 (2H, m), 2.54 (1H, m), 2.80 (2H, d), 8.0 (3H, br s).



(b) In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (32 mg) and C-cyclobutylmethylamine hydrochloride (13 mg) afforded the title compound (28 mg).

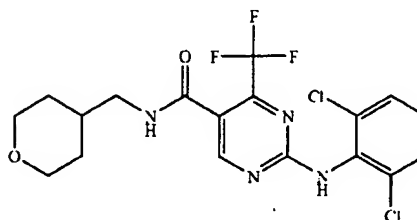
NMR (DMSO- d_6) δ 1.70 (2H, m), 1.82 (2H, m), 2.00 (2H, m), 2.50 (1H, m), 3.26 (2H, m), 7.08-7.95 (4H, m), 8.55 (1H, t), 8.77 (1H, s), 10.60 (1H, s).

LC/MS. t_r 3.56 min. [MH⁺] 385.



EXAMPLE 55

2-(2,6-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



In a manner similar to Reference Example 1(c) 2-(2,6-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-car-

US 7,635,701 B2

51

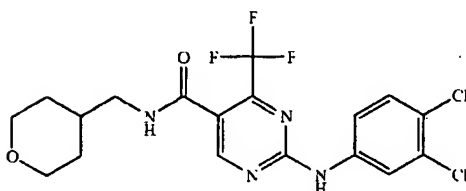
boxylic acid (30 mg) and 4-aminomethyltetrahydropyran (20 mg, ex CombiBlocks) afforded the title compound (32 mg)

NMR (DMSO-d₆) δ 1.16-1.22 (2H, m), 1.58 (2H, d), 1.70 (1H, m), 3.09 (2H, t), 3.23 (2H, m), 3.84 (2H, d), 7.38 (1H, t), 7.59 (2H, d), 8.61 (2H, m), 10.10 (1H, s)

LC/MS, t_r 3.02 min. Molecular ion observed (MH⁺)=449 consistent with the molecular formula C₁₈H₁₇³⁵Cl₂F₃N₄O₂

EXAMPLE 56

2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



In a manner similar to Reference Example 1(c) 2-(3,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (30 mg) and 4-aminomethyltetrahydropyran (20 mg, ex CombiBlocks) afforded the title compound (38 mg).

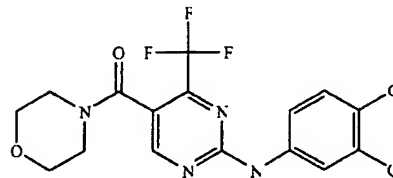
NMR (DMSO-d₆) δ 1.18-1.25 (2H, m), 1.62 (2H, d), 1.74 (1H, m), 3.1 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.60 (1H, t), 7.69 (1H, m), 8.16 (1H, dd), 8.64 (1H, t), 8.84 (1H, s), 10.70 (1H, s)

52

LC/MS, t_r 3.45 min. Molecular ion observed (MH⁺)=449 consistent with the molecular formula C₁₈H₁₇N₄O₂³⁵Cl₂F₃

EXAMPLE 68

1-[2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-(morpholin-4-yl)-methanone



In a manner similar to Reference Example 1(c) 2-(3,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (30 mg) and morpholine (15 mg, ex Aldrich) afforded the title compound (36 mg).

NMR (DMSO-d₆) δ 3.7 (8H, s), 7.65 (1H, d), 7.75 (1H, dd), 8.2 (1H, d), 8.9 (1H, s), 10.80 (1H, s)

LC/MS, t_r 3.45 min. Molecular ion observed (MH⁺)=421 consistent with the molecular formula C₁₆H₁₃N₄O₂³⁵Cl₂F₃

Table 2:

Example 57-67 and 69-73 were prepared in a corresponding fashion to the above compounds.

TABLE 2

Compound Name	Structure	Mass spec details 1 Retention Time 2 MH ⁺ 3 Formula consistent with MH ⁺
57 2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cycloheptylamide		3.78 413 C ₁₉ H ₁₂ ³⁵ ClF ₃ N ₄ O
58 2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid [(S)-1-(tetrahydro-furan-2-yl-methyl)]-amide		3.25 401 C ₁₇ H ₁₆ ³⁵ ClF ₃ N ₄ O ₂

US 7,635,701 B2

53

54

TABLE 2-continued

Compound Name	Structure	Mass spec details 1 Retention Time 2 MH ⁺ 3 Formula consistent with MH ⁺
59 2-(3-Fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid [(S)-1-(tetrahydro-furan-2-yl)methyl]-amide		3.10 385 C ₁₇ H ₁₆ F ₄ N ₄ O ₂
60 2-(3-Bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid [(S)-1-(tetrahydro-furan-2-yl)methyl]-amide		3.29 447 C ₁₇ H ₁₆ ⁸¹ BrF ₃ N ₄ O ₂
61 2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (1-methanesulfonyl-piperidin-4-ylmethyl)-amide		3.22 492 C ₁₆ H ₂₁ ³⁵ ClF ₃ N ₅ O ₃ S
62 2-(2,5-Dichloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		3.90 447 C ₁₉ H ₁₉ ³⁵ Cl ₂ F ₃ N ₄ O
63 2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (1-ethyl-propyl)-amide		3.60 387 C ₁₇ H ₁₈ ³⁵ ClF ₃ N ₄ O

US 7,635,701 B2

55

56

TABLE 2-continued

Compound Name	Structure	Mass spec details 1 Retention Time 2 MH ⁺ 3 Formula consistent with MH ⁺
64 2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tert-butyl)-amide		3.55 373 C ₁₈ H ₁₆ ³⁵ ClF ₃ N ₄ O
65 2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-yl)-amide		3.18 401 C ₁₇ H ₁₆ ³⁵ ClF ₃ N ₄ O ₂
66 2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexyl-amide		3.67 399 C ₁₈ H ₁₈ ³⁵ ClF ₃ N ₄ O
67 1-[2-(3,5-Dichloro-phenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-1-(piperidin-1-yl)-methanone		3.84 419 C ₁₇ H ₁₅ ³⁵ Cl ₂ F ₃ N ₄ O
69 2-Phenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid (2,2-dimethyl-propyl)-amide		3.48 353 C ₁₇ H ₁₉ F ₃ N ₄ O

US 7,635,701 B2

57

58

TABLE 2-continued

Compound Name	Structure	Mass spec details 1 Retention Time 2 MH ⁺ 3 Formula consistent with MH ⁺
70 2-Phenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid (3,3-dimethyl-butyl)-amide		3.60 367 C ₁₈ H ₂₁ F ₃ N ₃ O
71 2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (piperidin-4-ylmethyl)-amide trifluoroacetate		2.46 414 C ₁₈ H ₁₉ ³⁵ ClF ₃ N ₃ O
72 1-[2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-1-(piperazin-1-yl)-methanone		2.42 386 C ₁₆ H ₁₅ ³⁵ ClF ₃ N ₅ O
73 2-(3-Fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid [(R)-1-(tetrahydro-furan-2-yl)methyl]-amide		3.10 385 C ₁₇ H ₁₆ F ₃ N ₃ O ₂

Table 3

Compounds 74 to 87 were prepared according to the conditions described for table 1, and purified by the method given in column P as follows:

Method A: refers to the procedure in part (b) of Example 166.

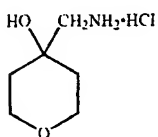
Method B: Mass-directed autopurification using the procedures detailed at the beginning of the experimental

US 7,635,701 B2

59

Method C' Purification using Biotage Chromatography over Merck 9385 Silica Gel (25 g) eluting with 1-2% methanol in dichloromethane.

Intermediate A: 4-Aminomethyltetrahydropyran-4-ol hydrochloride



60

To a solution of 1.0M lithium aluminium hydride in tetrahydrofuran (20 ml) was added under a nitrogen atmosphere a solution of 4-hydroxytetra-hydropyran-4-carbonitrile (0.50 g, prepared as described in Eiden et al., Arch. Pharm., 320, 348, (1987)) in tetrahydrofuran (2 ml) and the solution stirred at reflux for 6 hours. Water (1 ml) and 2N sodium hydroxide solution (1 ml) were added cautiously and the resultant solid filtered and washed with ether. The filtrate was dried (MgSO₄), evaporated and the residue dissolved in ethanol (3 ml) and concentrated hydrochloric acid (0.5 ml) added. Solvent was removed under reduced pressure and the resultant solid washed with ether and dried in vacuo at 40° C. to afford the title compound (234 mg).

NMR (DMSO-d₆) 1.45-1.6 (4H, m), 2.78 (2H, q), 3.61 (4H, m), 5.07 (1H, br s), 7.89 (3H, br s).

			LC/MS
			1 Retention time (min)
			2 MH ⁺
			P 3 Formula
74	3,4-Dichloro-aniline (Lancaster)	Cyclopentylamine (Aldrich)	3,4-Dichlorophenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylamide
			A 3.53 419 C ₁₇ H ₁₅ ³⁵ Cl ₂ F ₃ N ₄ O
75	3,5-Dichloro-aniline (Lancaster)	Cyclopentylamine (Aldrich)	3,5-Dichlorophenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylamide
			A 3.60 419 C ₁₇ H ₁₅ ³⁵ Cl ₂ F ₃ N ₄ O
76	3-Methoxy-aniline (Lancaster)	Cyclopentylamine (Aldrich)	3-Methoxyphenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylamide
			A 3.08 381 C ₁₈ H ₁₉ F ₃ N ₄ O ₂

US 7,635,701 B2

61

62

-continued

Ex 1	2	3-Product	LC/MS 1 Retention time (min) 2 MH ⁺ P 3 Formula
77 2,3-Dichloro-aniline (Lancaster)	Cyclopentylamine (Aldrich)	2,3-Dichlorophenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylamide	A 3.60 419 $C_{17}H_{15}^{35}Cl_2$ F_3N_4O
78 3-fluoro-aniline (Lancaster)	Pipendine (Aldrich)	1-[2-(3-fluorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-1-pipendin-1-yl-methanone	A 3.39 369 $C_{17}H_{16}N_4F_4O$
79 3-chloro-aniline (Lancaster)	1-methanesulfonyl-piperazine (CS 5081147)	1-[2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-1-(4-methanesulfonyl-piperazin-1-yl)-methanone	A 3.21 464 $C_{17}H_{17}Cl^{35}F_3N_5$ O_3S
80 3-bromo-aniline (Lancaster)	R-1-(tetrahydrofuran-2-yl)methylamine (Lancaster)	2-(3-bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid [R-1-(tetrahydrofuran-2-yl)methyl]-amide	A 3.29 447 $C_{17}H_{16}^{81}Br$ $F_3N_4O_2$
81 2,3-dichloro-aniline	tetrahydro-thiopyran-4-ylamine JOC 46(22), 4376-83 1981	2-(2,3-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-thiopyran-4-yl)-amide	C 3.74 451 $C_{17}H_{15}^{35}Cl_2F_3$ N_4OS
82 2,3-dichloro-aniline	(1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)amine hydrochloride WO 0218380	2-(2,3-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)-amide	C 3.29 483 $C_{17}H_{15}^{35}$ $Cl_2F_3N_4O_3S$

US 7,635,701 B2

63

64

-continued

Ex 1	2	3-Product	LC/MS 1 Retention time (min) 2 MH ⁺ P 3 Formula
83 3-fluoro-aniline (Lancaster)	cyclopropyl-methyl-amine (Lancaster)	2-(3-Fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopropylmethyl-amide	A 3.32 355 C ₁₆ H ₁₄ F ₄ N ₄ O
84 3-chloro-aniline (Lancaster)	cyclopropyl-methyl-amine (Lancaster)	2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopropylmethyl-amide	B 3.46 371 C ₁₆ H ₁₄ ³⁵ ClF ₃ N ₄ O
85 2,5-Di-chloro-aniline (ex Lancaster)	Morpholine (ex Aldrich)	1-[2-(2,5-Dichloro-phenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-1-piperidin-1-yl-methanone	A 3.64 419 C ₁₇ H ₁₅ ³⁵ Cl ₂ F ₃ N ₄ O
86 3-Fluoro-aniline (ex Lancaster)	1-Amino-methyl-1-cyclohexanol hydrochloride (ex Aldrich)	2-(3-Fluorophenyl-amino)-4-trifluoro-methyl-pyrimidine-5-carboxylic acid(1-hydroxy-cyclohexyl-methyl)amide	A 3.25 411 C ₁₉ H ₂₀ F ₄ N ₄ O ₂
87 3-Bromo-aniline (ex Lancaster)	4-Amino-methyl-tetrahydro-4H-pyran-4-ol hydrochloride (Intermediate A)	2-(3-Bromophenyl-amino)-4-trifluoro-methyl-pyrimidine-5-carboxylic acid (4-hydroxytetrahydropyran-4-ylmethyl)amide	A 3.05 473 C ₁₈ H ₁₈ ⁷⁹ B: F ₃ N ₄ O ₃

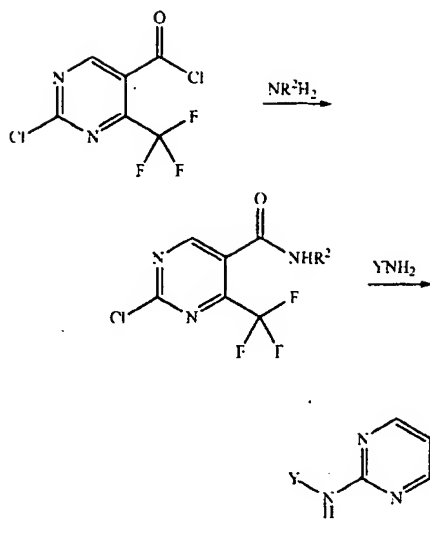
Table 4

In the following table 4, column 2 gives precursors R²NH₂ 65 that were reacted with 2-chloro (trifluoromethyl)pyrimidine-5-carboxyl chloride in a manner similar to that in part (a) of

Example 166. The resultant product was reacted with the precursor YNH₂ of column 3 in a manner similar to that in part (b) of Example 166, to provide the final product in column 4.

US 7,635,701 B2

65



66

Preparation Method A: refers to the procedure give in part (b) of Example 166.

Preparation Method B: This is exemplified by the by Example 109. 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)amide (50 mg) and 2-chloro-2-cyanoaniline (118 mg) were irradiated in a microwave apparatus (the model used was the 'Creator', supplied by 'Personal Chemistry', operating at 300 Watts), at 190° C. for 30 min. For examples using this method, the equivalents of substituted aniline YNH₂ used, and duration of irradiation follow in brackets after the method B.

The column entitled "Prep" refers to the preparation method used.

The product was then purified according to on of the following methods described below. The column entitled "Pure" refers to the purification method used

Purification method A: refers to the procedure give in part (b) of Example 166

Purification method B: mass directed autopurification using the procedures detailed at the beginning of the experimental.

Purification method C: The reaction was worked up as for part (b) of Example 166, and the crude product further purified by Biotage chromatography over Merck 9385 silica gel, eluting with isohexane/ethyl acetate.

TABLE 4

8R	Cyclohexanemethylamine	NR ² H ₂	YNH ₂	Compound	Prep	Pure	Structure	with MH ⁺	LCMS 1 Retention time 2 MH ⁺ 3 Formula consistent
8R	Cyclohexanemethylamine (Aldrich)		3,5-Bis-trifluoromethyl-phenylamine (Aldrich)	2-(3,5-Bis-trifluoromethyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethylamide	A	B		4.09 515 C ₂₁ H ₁₉ F ₉ N ₄ O	
9	Cyclohexanemethylamine		5-Aminoisophthalonitrile	2-(3,5-Dicyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethylamide	A	B		3.59 429 C ₂₁ H ₁₈ F ₃ N ₄ O	

US 7,635,701 B2

67

68

TABLE 4-continued

							LCMS 1 Retention time 2 MH ⁺ 3 Formula consistent
	Cyclo- hexanemet hanamine NR ² H ₂	YNH ₂	Compound	Prep	Pure	Structure	with MH ⁺
90	Cyclo- hexanemet hanamine	3-Fluoro- 5-tri- fluoro- methyl- phenyl- amine (Supplier Apollo)	2-(3-Fluoro- 5-trifluoro- methyl- phenylamino)- 4-trifluoro- methyl- pyrimidine-5- carboxylic acid cyclohexyl- methyl- amide	A	B		3.96 465 C ₂₀ H ₁₉ F ₇ N ₃ O
91	Cyclo- hexanemet hanamine	3-Bromo- 5-tri- fluoro- methyl- phenyl- amine (Supplier Avacade)	2-(3-Bromo- 5-trifluoro- methyl- phenylamino)- 4-trifluoro- methyl- pyrimidine-5- carboxylic acid cyclohexyl- methyl- amide	A	B		4.13 524 C ₂₀ H ₁₇ BrF ₆ N ₃ O
92	Cyclo- hexanemet hanamine	2-Chloro- 3-methyl- phenyl- amine (WO 97/41846- hydro- genate 2- chloro-3- nitroto- luene)	2-(2-Chloro-3- methyl- phenylamino)- 4-trifluoro-me- thyl- pyrimidine-5- carboxylic acid cyclohexyl- methyl- amide	A	B		3.82 427 C ₂₀ H ₂₂ ClF ₃ N ₃ O
93	Cyclo- hexanemet hanamine	3-Chloro- 2-methyl- phenyl- amine (Supplier Aldrich)	2-(3-Chloro- 2-methyl- phenylamino)- 4-trifluoro- methyl- pyrimidine- 5-carboxylic acid	A	B		3.76 427 C ₂₀ H ₁₇ ClF ₃ N ₃ O
94	Cyclo- hexanemet hanamine	4-Chloro- 2-methyl- phenyl- amine (Supplier Aldrich)	2-(4-Chloro- 2-methyl- phenylamino)- 4-trifluoro- methyl- pyrimidine- 5-carboxyl acid cyclohexyl- methyl- amide	A	B		3.77 427 C ₂₀ H ₂₂ ClF ₃ N ₃ O

US 7,635,701 B2

69

70

TABLE 4-continued

	Cyclohexanemethanamine NR ² H ₂	YNH ₂	Compound	Prep	Pure	Structure	LCMS 1 Retention time 2 MH ⁺ 3 Formula consistent with MH ⁺
95	Cyclohexanemethanamine	4-Chloro-2,6-dimethylphenylamine (Supplier Davos)	2-(4-Chloro-2,6-dimethylphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid	A	B		3.79 441 C ₂₁ H ₂₄ ³⁵ ClF ₃ N ₄ O
96	Cyclopentylmethanamine	3,5-difluoroaniline (Aldrich)	2-(3,5-Difluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid	A	C		3.70 401 C ₁₈ H ₁₇ F ₅ N ₄ O
97	Cyclopentylmethanamine	3-Fluoro-4-(trifluoromethyl)aniline (Fluorochem)	2-(4-Trifluoromethyl-3-fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid	A	B		3.86 451 C ₁₉ H ₁₇ F ₅ N ₄ O
98	4-Aminomethyltetrahydropyran (Combi-Blocks)	2,4-Difluoroaniline (Lancaster)	2-(2,4-Difluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid	A	A		3.03 417 C ₁₈ H ₁₇ F ₅ N ₄ O ₂
99	4-Aminomethyltetrahydropyran (Combi-Blocks)	2-Fluoro-4-chloroaniline (Lancaster)	2-(2-Fluoro-4-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid	A	A		3.23 433 C ₁₈ H ₁₇ ³⁵ ClF ₄ N ₄ O ₂

US 7,635,701 B2

71

72

TABLE 4-continued

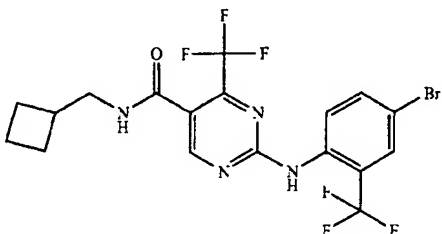
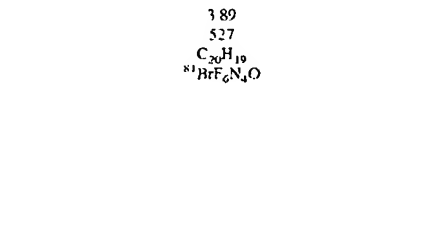
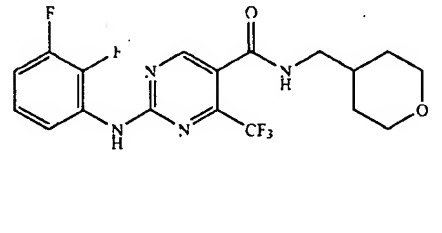
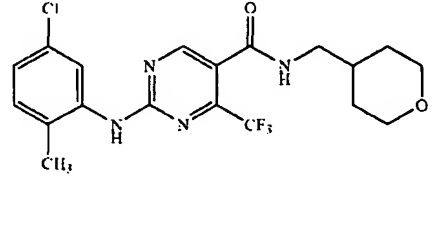
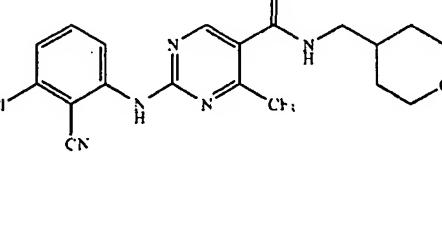
	Cyclohexanecarboxamide NR ² II ₂	YNII ₂	Compound	Prep	Pure	Structure	LCMS 1 Retention time 2 MH ⁺ 3 Formula consistent with MH ⁺
100	Cyclohexanecarboxamide (Lancaster)	2-Trifluoromethyl-4-fluoroaniline (Lancaster)	2-(2-Trifluoromethyl-4-fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylmethylamide	A	B		3.69 465 C ₂₆ H ₁₉ F ₇ N ₃ O
101	Cyclobutanecarboxamide	2-Trifluoromethyl-4-fluoroaniline (Lancaster)	2-(2-Trifluoromethyl-4-fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclobutylmethylamide	A	B		3.49 437 C ₁₈ H ₁₅ F ₇ N ₃ O
102	Cyclobutanecarboxamide	2-Chloro-4-trifluoromethylaniline (Lancaster)	2-(2-Chloro-4-trifluoromethylphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclobutylmethylamide	A	B		3.79 453 C ₁₈ H ₁₅ ³⁵ ClF ₆ N ₃ O
103	Cyclobutanecarboxamide	2-Chloro-4-cyanoaniline (Lancaster)	2-(2-Chloro-4-cyanophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclobutylmethylamide	B	C		3.47 410 C ₁₈ H ₁₅ ³⁵ ClF ₃ N ₃ O
104	4-Amino-2-methyl-2H-tetrahydropyran (Combi-Blocks)	2-Trifluoromethyl-4-chloroaniline (Lancaster)	2-(2-Trifluoromethyl-4-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-2H-pyran-4-ylmethyl)amide	A	A		3.34 483 C ₁₉ H ₁₇ ³⁵ ClF ₆ N ₃ O ₂

US 7,635,701 B2

73

74

TABLE 4-continued

							1 CMS 1 Retention time 2 MH ⁺ 3 Formula consistent
	Cyclo- hexanemet hanamine	YNH ₂	Compound	Prep	Pure	Structure	with MH ⁺
105	Cyclo- butyl- methyl- amine	2-Tri- fluoro- methyl- 4-bromo- aniline (Lan- caster)	2-(2-Trifluoro- methyl-4- bromophenyl- amino)-4- trifluoro- methyl- pyrimidine-5- carboxylic acid cyclobutyl- methyl- amide	B (5 equiv. 45 min)	B		3.71 499 C ₁₈ H ₁₅ ⁸¹ BrF ₆ N ₄ O
106	Cyclo- hexyl- methyl- 4-bromo- aniline (Lan- caster)	2-Tri- fluoro- methyl- 4-bromo- aniline (Lan- caster)	2-(2-Trifluoro- methyl-4- bromophenyl- amino)-4- trifluoromethyl- pyrimidine-5- carboxylic acid cyclohexyl- methyl- amide	B (2.5 equiv. 45 min)	B		3.89 527 C ₂₀ H ₁₉ ⁸¹ BrF ₆ N ₄ O
107	4-Amino- methyl- tetra- hydro-nl pyran (ex Combi Blocks)	2,3-Di- fluoro- aniline (ex Aldrich)	2-(2,3-Difluoro- phenyl- amino)-4- trifluoro- methyl-pyri- midine-5- carboxylic acid (tetrahydro- pyran-4-yl- methyl)-amide	A	B		3.64 417 C ₁₈ H ₁₇ F ₃ N ₄ O ₂
108	4-Amino- methyl- tetra- hydro-nl pyran (ex Combi Blocks)	5-Chloro- 2-methyl- aniline (ex Aldrich)	2-(5-Chloro-2- methyl-phenyl- amino)-4-tri- fluoromethyl- pyrimidine-5- carboxylic acid (tetrahydro- pyran-4-yl- methyl)-amide	A	B		3.64 429 C ₁₉ H ₁₇ Cl ₂ ³⁵ ClF ₃ N ₄ O ₂
109	4-Amino- methyl- tetra- hydro-nl pyran (ex Combi Blocks)	3-Chloro- 2-cyano- aniline (ex Lan- caster)	2-(3-Chloro-2- cyano-phenyl- amino)-4-tri- fluoromethyl- pyrimidine-5- carboxylic acid (tetrahydro- pyran-4-yl- methyl)-amide	B	B		3.64 440 C ₁₉ H ₁₇ ³⁵ ClF ₃ N ₄ O ₂

US 7,635,701 B2

75

76

TABLE 4-continued

	Cyclohexanemethanamine NR ³ H ₂	YNH ₂	Compound	Prep	Pure	Structure	1 CMS 1 Retention time 2 MH ⁺ 3 Formula consistent with MH ⁺
110	4-Amino- methyl- tetra- hydro-nl pyran (ex Combi Blocks)	2-Chloro- 4-methyl- aniline	2-(2-Chloro-4- methyl-phenyl- amino)-4-tri- fluoromethyl- pyrimidine-5- carboxylic acid (tetrahydro- pyran-4-yl- methyl)-amide	A	B		3.27 429 C ₁₉ H ₂₀ ³⁵ ClF ₃ N ₄ O ₂
111	4-Amino- methyl- tetra- hydro-nl pyran (ex Combi Blocks)	4-Chloro- 3-cyano- aniline	2-(4-Chloro-3- cyano-phenyl- amino)-4-tri- fluoromethyl- pyrimidine-5- carboxylic acid (tetrahydro- pyran-4-yl- methyl)-amide	A	B		3.22 429 C ₁₉ H ₂₀ ¹⁵ ClF ₃ N ₄ O ₂
112	4-Amino- methyl- tetra- hydro-nl pyran (ex Combi Blocks)	4-Chloro- 3-cyano- aniline	2-(4-Chloro-3- cyano-phenyl- amino)-4-tri- fluoromethyl- pyrimidine-5- carboxylic acid (tetrahydro- pyran-4-yl- methyl)-amide	A	B		3.22 440 C ₁₉ H ₁₇ ³⁵ ClF ₃ N ₄ O ₂
113	4-Amino- methyl- tetra- hydro-nl pyran (ex Combi Blocks)	2-Chloro-5- methyl- aniline (ex Aldrich)	2-(2-Chloro-5- methyl-phenyl- amino)-4-tri- fluoromethyl- pyrimidine-5- carboxylic acid (tetrahydro- pyran-4-yl- methyl)-amide	A	B		3.28 429 C ₁₉ H ₂₀ ³⁵ ClF ₃ N ₄ O ₂
257	(Cyclo- butyl- methyl- amine	2-Chloro- aniline	2-(2-Chloro- phenyl- amino)-4-tri- fluoro- methyl-pyri- midine-5-car- boxylic acid cyclobutyl- methyl- amid	C	B		3.52 385 C ₁₇ H ₁₆ ³⁵ ClF ₃ N ₄ O

US 7,635,701 B2

77

78

TABLE 4-continued

	Cyclohexanemethanamine NR ² H ₂	YNH ₂	Compound	Prep	Pure	Structure	LCMS 1 Retention time 2 MH ⁺ 3 Formula consistent with MH ⁺
258	(Cyclobutylmethyl)amine	3-Fluoro-5-trifluoromethylaniline	2-(3-Fluoro-5-trifluoromethylphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclobutylmethylamide	C	B		3.80 4.37 C ₁₈ H ₁₅ F ₇ N ₄ O
259	(Cyclobutylmethyl)amine	5-Chloro-2-methylaniline	2-(5-Chloro-2-methylphenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclobutylmethylamide	C	B		3.61 3.99 C ₁₈ H ₁₄ 3-ClF ₃ N ₄ O

**In Example 103 - Preparation Method B (5 equiv, 15 min)

N.B. Reaction mixture also contained 0.5 ml MeCN and purification method C. The product was purified by trituration with isohexane after this Method C - As for method B, but the solvent used was 1,4-dioxan not MeCN

TABLE 5

Compound Name	Structure	Purification method	Mass spec details 1 Retention Time 2 MH ⁺ 3 Formula consistent with MH ⁺
114 3-Fluorophenylamino-4-trifluoromethylpyrimidine-5-carboxylic acid cyclopentylamide		A	3.23 3.69 C ₁₇ H ₁₆ F ₄ N ₄ O

US 7,635,701 B2

79

80

TABLE 5-continued

Compound Name	Structure	Purification method	Mass spec details 1 Retention Time 2 MH ⁺ 3 Formula consistent with MH ⁺
115 2,6-Dichlorophenylamino-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentyl-amide		A	3.17 419 C ₁₇ H ₁₅ ³⁵ Cl ₂ F ₃ N ₄ O
116 3-Chlorophenylamino-4-trifluoromethylpyrimidine-5-carboxylic acid (2-ethylbutyl)-amide		A	3.79 401 C ₁₈ H ₂₀ ³⁵ ClF ₃ N ₄ O
117 2-Phenylamino-4-trifluoromethyl-pyrimidin-5-carboxylic acid (2-methoxy-ethyl)-amide		A	2.98 339 C ₁₅ H ₁₅ F ₃ N ₄ O ₂
118 2-Phenylamino-4-trifluoromethyl-pyrimidin-5-carboxylic acid [2-(dimethyl-amino)ethyl]-amide		A	2.32 354 C ₁₆ H ₁₈ F ₃ N ₅ O

US 7,635,701 B2

81

82

TABLE 5-continued

Compound Name	Structure	Purification method	Mass spec details	
			1 Retention Time	2 MH ⁺
			3 Formula consistent with MH ⁺	
119 1-[2-(3-Chlorophenyl-amino)-4-trifluoro-methylpyrimidin-5-yl]-1-(4-methoxypiperin-1-yl)-methanone		A	3.33 415 C ₁₈ H ₁₈ ³⁵ ClF ₃ N ₄ O ₂	
120 1-[2-(3-Chlorophenyl-amino)-4-trifluoro-methylpyrimidin-5-yl]-1-(1,1-dioxothiomorpholin-4-yl)-methanone		A	3.16 435 C ₁₆ H ₁₄ ³⁵ ClF ₃ N ₄ O ₂ S	
121 N-[(R)-1-[1-[2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanoyl]-pyrrolidin-3-yl]-acetamide		A	2.91 428 C ₁₈ H ₁₇ ³⁵ ClF ₃ N ₅ O ₂	
122 N-[(S)-1-[1-[2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanoyl]-pyrrolidin-3-yl]-acetamide		A	2.91 428 C ₁₈ H ₁₇ ³⁵ ClF ₃ N ₅ O ₂	

US 7,635,701 B2

83

84

TABLE 5-continued

Compound Name	Structure	Purification method	Mass spec details	
			1 Retention Time	2 MH ⁺
			3 Formula consistent with MH ⁺	
123 1-{1-[2-(3-Chloro-phenylamino)-4-trifluoromethyl-pyrimidin-5-yl]-methanoyl}-piperidine-4-carboxylic acid methylamide		C Sol 1	2.98 442	C ₁₉ H ₁₉ ³⁵ ClF ₃ N ₅ O ₂
124 2-(3-Chlorophenyl-amino)-4-trifluoromethylpyrimidine-5-carboxylic acid (4-hydroxytetrahydropyran-4-ylmethyl)-amide		A	3.60 429	C ₁₈ H ₁₈ ³⁵ ClF ₃ N ₄ O ₄
125 2-(3-Fluorophenyl-amino)-4-trifluoromethylpyrimidine-5-carboxylic acid (1-hydroxytetrahydropyran-4-ylmethyl)-amide		A	2.86 413	C ₁₈ H ₁₈ F ₄ N ₄ O ₄
126 1-[2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidin-5-yl]-1-(4-methylpiperazin-1-yl)-methanone		A	2.53 400	C ₁₇ H ₁₇ ³⁵ ClF ₃ N ₅ O

US 7,635,701 B2

85

86

TABLE 5-continued

Compound Name	Structure	Purification method	Mass spec details 1 Retention Time 2 MH ⁺ 3 Formula consistent with MH ⁺
127 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (2-methoxy-ethyl)-amide		A	3.23 375 C ₁₅ H ₁₄ ³⁵ ClF ₃ N ₄ O ₂
128 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (2-dimethylamino-ethyl)-amide		A	2.51 388 C ₁₆ H ₁₇ ³⁵ ClF ₃ N ₄ O
129 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid [R-1-(tetrahydrofuran-2-yl)methyl]-amide		A	3.25 401 C ₁₇ H ₁₆ ³⁵ ClF ₃ N ₄ O ₂
130 2-(Phenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-pyran-4-yl)methyl)-amide		A	3.01 381 C ₁₈ H ₁₉ F ₃ N ₄ O ₂

US 7,635,701 B2

87

88

TABLE 5-continued

Compound Name	Structure	Purification method	Mass spec details	
			1 Retention Time	2 MH ⁺
			3 Formula consistent with MH ⁺	
131 2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylamide		C Sol 2	3.74 433	C ₁₈ H ₁₇ ³⁵ Cl ₂ F ₃ N ₄ O
132 2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylamide		A	3.56 383	C ₁₈ H ₁₈ F ₄ N ₄ O
133 2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylamide		A	3.74 445	C ₁₈ H ₁₈ ⁸¹ BrF ₃ N ₄ O
134 2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-yl)-amide		A	3.06 385	C ₁₇ H ₁₆ F ₄ N ₄ O ₂

US 7,635,701 B2

89

90

TABLE 5-continued

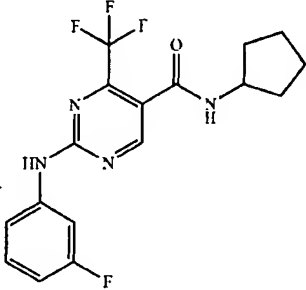
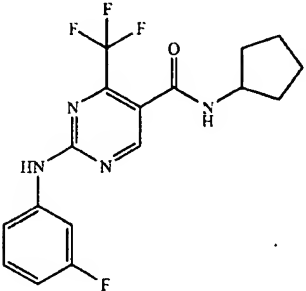
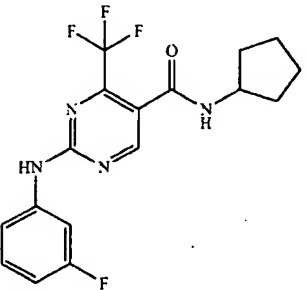
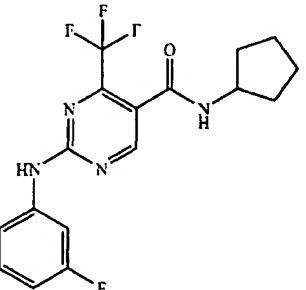
Compound Name	Structure	Purification method	Mass spec details	
			1 Retention Time	2 MH ⁺
			3 Formula consistent with MH ⁺	
135 2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-yl)-amide		A	3.25 4.47	C ₁₇ H ₁₆ ⁸¹ BrF ₃ N ₄ O ₂
136 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-yl)-amide		A	3.33 4.35	C ₁₇ H ₁₄ ³⁵ Cl ₂ F ₃ N ₄ O ₂
137 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylamide		A	3.79 4.33	C ₁₈ H ₁₇ ³⁵ Cl ₂ F ₃ N ₄ O
138 2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid cyclohexylamide		A	3.90 4.33	C ₁₈ H ₁₇ ³⁵ Cl ₂ F ₃ N ₄ O

US 7,635,701 B2

91

92

TABLE 5-continued

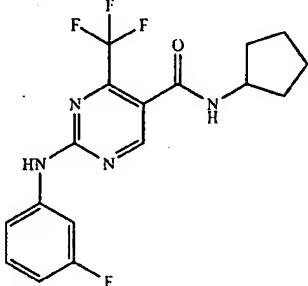
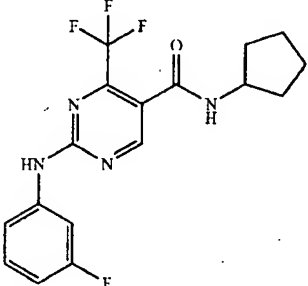
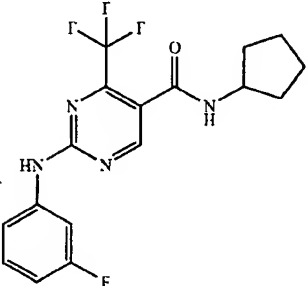
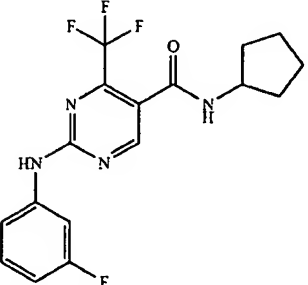
Compound Name	Structure	Purification method	Mass spec details	
			1 Retention Time	2 MH ⁺
			3 Formula consistent with MH ⁺	
139 2-(2,3-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-yl)-amide		A	3.26 435	C ₁₇ H ₁₈ ³⁵ Cl ₂ F ₃ N ₄ O ₂
140 2-(3-Fluorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydrothiopyran-4-yl)-amide		C Sol 2	3.37 401	C ₁₇ H ₁₆ F ₄ N ₄ OS
141 2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydrothiopyran-4-yl)-amide		C Sol 2	3.51 417	C ₁₇ H ₁₆ ³⁵ ClF ₃ N ₄ OS
142 2-(3-Bromophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydrothiopyran-4-yl)-amide		C Sol 2	3.55 463	C ₁₇ H ₁₆ ⁸¹ BrF ₃ N ₄ OS

US 7,635,701 B2

93

94

TABLE 5-continued

Compound Name	Structure	Purification method	Mass spec details 1 Retention Time 2 MH ⁺ 3 Formula consistent with MH ⁺
143 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydrothiopyran-4-yl)-amide		C Sol 2	3.61 451 C ₁₇ H ₁₅ ³⁵ Cl ₂ F ₃ N ₄ OS
144 2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydrothiopyran-4-yl)-amide		C Sol 2	3.72 451 C ₁₇ H ₁₅ ³⁵ Cl ₂ F ₃ N ₄ OS
145 2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (1,1-dioxohexahydro-1H-thiopyran-4-yl)-amide		C Sol 3	3.32 483 C ₁₇ H ₁₅ ³⁵ Cl ₂ F ₃ N ₄ O ₂ S
260 3-Chlorophenylamino-4-trifluoromethylpyrimidine-5-carboxylic acid 2-(hydroxypropyl)amide		A	3.69 375 C ₁₅ H ₁₄ ³⁵ ClF ₃ N ₄ O ₂

Compounds 114 to 145 were prepared as set out for table 2 and purified as follows

Purification Method A. as for reference example 1c.

Purification Method C. The reaction was worked up as in example 1c, and the product purified by Biotage chromatography using the following solvent systems

Sol 1 ethyl acetate

Sol 2 1% methanol in dichloromethane

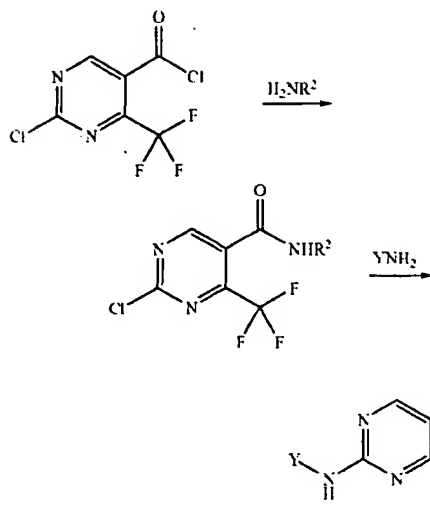
Sol 3 2% methanol in dichloromethane

US 7,635,701 B2

95

96

Table 6



Preparation Method A: refers to the procedure give in part (b) of Example 166.

Preparation Method B: Exemplified by Example 154: A mixture of 2-chloro-4-(trifluoromethyl)-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg), 3,5-dicyanoaniline (69 mg), and acetonitrile (0.5 ml) was irradiated in a microwave apparatus (the model used was the 'Creator', supplied by 'Personal Chemistry', operating at 300 Watts), at 180° C. for 60 min. The temperature, duration of irradiation, and number of equivalents of the substituted-aniline used are given after the method in the table.

Preparation Method C: exemplified by Example 162: A mixture of 2-chloro-4-(trifluoromethyl)-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (80 mg) and 4-fluoro-2-(trifluoromethyl)aniline (111 mg) was irradiated in microwave apparatus (the model used was the 'Creator', supplied by 'Personal Chemistry', operating at 300 Watts), at 190° C. for 45 min.

Purification was carried out as detailed in the table to give the product.

Purification Method A: refers to the procedure give in part (b) of Example 166.

Purification Method B: mass directed autopurification using the procedures detailed at the beginning of the experimental.

Purification Method C: The reaction was worked up as for part (b) of Example 166, and the crude product further purified by Biotage chromatography over Merck 9385 silica gel, eluting with isohexane/ethyl acetate (7:3).

TABLE 6

Ex	Compound Name	Structure	Preparation Method	Purification method	LCMS 1 Retention time (min) 2 MH ⁺ 3 Consistent Formula
146	2-(3-Methoxy-5-trifluoromethyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		A	B	3.91 477 C ₂₁ H ₂₂ F ₆ N ₄ O ₂
147	2-(4-Chloro-3-methyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		A	B	3.96 427 C ₂₀ H ₂₂ ³⁵ ClF ₃ N ₄ O
148	2-(3-Chloro-4-methyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid N-cyclohexylmethyl-amide		A	B	3.92 427 C ₂₀ H ₂₂ ³⁵ ClF ₃ N ₄ O
149	2-(4-Chloro-3-cyano-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		A	B	3.76 438 C ₂₀ H ₁₉ ³⁵ ClF ₃ N ₅ O

US 7,635,701 B2

97

98

TABLE 6-continued

Ex	Compound Name	Structure	Preparation Method	Purification method	LC/MS 1 Retention time (min) 2 MII* 3 Consistent formula
150	2-(2-Chloro-5-methyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		A	B	3.82 427 $C_{23}H_{22}^{35}ClF_3N_4O$
151	2-(3-Chloro-2,6-dimethyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		A	B	3.76 441 $C_{21}H_{24}^{40}ClF_3N_4O$
152	2-(3-Chloro-4-trifluoromethoxyphenyl-amino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		A	A	4.00 497 $C_{20}H_{19}^{35}ClF_6N_4O_2$
153	2-(3-Fluoro-4-trifluoromethylphenyl-amino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		A	C	3.89 465 $C_{22}H_{19}F_7N_4O$
154	2-(3,5-Dicyano-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide		B (180°, 60 mins, 3 equiv)	B	3.01 431 $C_{20}H_{17}F_3N_6O_2$
155	2-(3-Chloro-2,6-dimethylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide		A	B	3.22 443 $C_{22}H_{27}^{45}ClF_3N_4O_2$
156	2-(2-Chloro-6-methyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide		B (180°, 60 mins, 5 equiv)	B	3.05 429 $C_{19}H_{20}^{45}ClF_3N_4O_2$
157	2-(2-Chloro-3-methyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide		A	B	3.27 429 $C_{15}H_{20}^{35}ClF_3N_4O_2$

US 7,635,701 B2

99

100

TABLE 6-continued

Ex	Compound Name	Structure	Preparation Method	Purification method	LC/MS 1 Retention time (min) 2 MII* 3 Consistent Formula
158	2-(4-Chloro-2,6-dimethylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide		A	B	3.26 443 $C_{20}H_{22}^{35}ClF_3N_4O_2$
159	2-(5-Chloro-2-sulfamoylphenyl-amino)-4-amino-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide		B (180°, 60 mins, 5 equiv)	B	3.08 494 $C_{18}H_{19}^{35}ClF_3N_5O_3S$
160	2-(2-Fluoro-4-trifluoromethylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide		A	A	3.67 437 $C_{18}H_{15}F_7N_4O$
161	2-(2-Chloro-4-trifluoromethylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide		A	B	3.97 481 $C_{20}H_{19}^{35}ClF_6N_4O$
162	2-(2-Trifluoromethyl-4-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)amide		C	B	3.16 467 $C_{19}H_{17}N_4O_3F_7$
261	2-(2-Fluoro-4-trifluoromethylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide		B (180°, 2 x 42 min, 5 equivalents)	B	3.37 467 $C_{19}H_{17}F_7N_4O_3$

US 7,635,701 B2

101

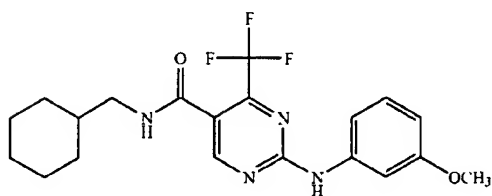
102

TABLE 6-continued

Ex	Compound Name	Structure	Preparation Method	Purification method	LCMS
					1 Retention time (min) 2 $M-H^+$ 3 Consistent formula
262	2-(3,5-Bis(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide		B 180°C 30 min 5 equivalents	B	Molecular ion observed $[M-H]^+$ 485 consistent with molecular formula $C_{19}H_{15}F_9N_4O$

EXAMPLE 163

2-(3-Methoxyphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



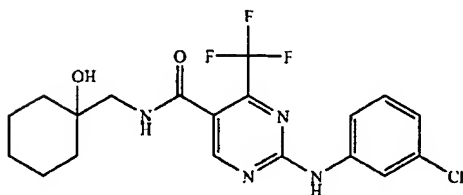
In a manner similar to Reference Example 1(c) 2-(3-methoxyphenylamino)-4-trifluoro-methylpyrimidine-5-carboxylic acid (32 mg) and cyclohexanemethanamine (16 μ l, ex Lancaster) afforded the title compound (28 mg).

NMR (DMSO- d_6) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.55-1.75 (5H, m), 3.06 (2H, t), 3.74 (3H, s), 6.63 (1H, d), 7.2-7.3 (2H, m), 7.54 (1H, s), 8.57 (1H, t), 8.74 (1H, s), 10.35 (1H, s).

LC/MS, t_r =3.57 min. Molecular ion observed $[M-H]^+$ =409 consistent with the molecular formula $C_{20}H_{23}F_3N_4O_2$.

EXAMPLE 164

2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (1-hydroxycyclohexylmethyl)-amide



In a manner similar to Reference Example 1(c) 2-(3-chlorophenylamino)-4-trifluoro-methylpyrimidine-5-carboxylic

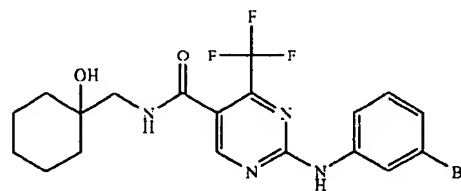
acid (32 mg) and 1-aminomethyl-1-cyclohexanol hydrochloride (20 mg, ex Aldrich) afforded the title compound (29 mg).

NMR (DMSO- d_6) δ 1.3 (1H, m), 1.4-1.5 (7H, m), 1.6 (2H, m), 3.28 (2H, d), 4.34 (1H, s), 7.16 (1H, d), 7.43 (1H, t), 7.73 (1H, d), 8.04 (1H, t), 8.51 (1H, t), 8.91 (1H, s), 10.65 (1H, s).

LC/MS, t_r =3.39 min. Molecular ion observed $[M-H]^+$ =427 consistent with the molecular formula $C_{19}H_{20}^{35}ClF_3N_4O_2$

EXAMPLE 165

2-(3-Bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (1-hydroxycyclohexylmethyl)-amide



In a manner similar to Reference Example 1(c) 2-(3-bromophenylamino)-4-trifluoro-methylpyrimidine-5-carboxylic acid (36.5 mg) and 1-aminomethyl-1-cyclohexanol hydrochloride (20 mg, ex Aldrich) afforded the title compound (28 mg).

NMR (DMSO- d_6) δ 1.25 (1H, m), 1.35-1.45 (7H, m), 1.6 (2H, m), 3.23 (2H, d), 4.28 (1H, s), 7.23 (1H, d), 7.31 (1H, t), 7.71 (1H, d), 8.12 (1H, s), 8.45 (1H, t), 8.85 (1H, s), 10.55 (1H, s).

LC/MS, t_r =3.43 min. Molecular ion observed $[M-H]^+$ =471 consistent with the molecular formula $C_{19}H_{20}^{79}BrF_3N_4O_2$.

US 7,635,701 B2

103

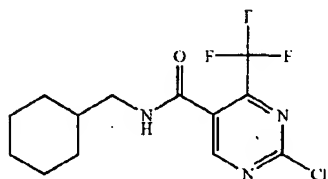
EXAMPLE 166

2-(3-Chloro-4-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide

(a). To a solution of 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (750 mg, ex Maybridge) in dichloromethane (15 ml) at -40°C was added dropwise over 30 minutes a solution of cyclohexylmethanamine (0.35 ml, ex Lancaster) and triethylamine (0.41 ml) in dichloromethane (15 ml). Dichloromethane was removed under reduced pressure and ethyl acetate (20 ml) added. The solution was washed sequentially with water, 5% sodium bicarbonate solution and water, dried (MgSO₄), evaporated and triturated with ether:hexane to afford 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (666 mg).

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.55-1.75 (5H, m), 3.12 (2H, t), 8.75 (1H, t), 9.18 (1H, s).

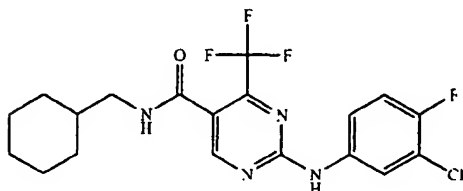
LC/MS, t=3.31 min. Molecular ion observed [MH⁺]=322 consistent with the molecular formula C₁₃H₁₅³⁵ClF₃N₃O.



(b) To a solution of 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (100 mg) in 1,4-dioxan (1 ml) was added 3-chloro-4-fluoroaniline (228 mg, ex Lancaster) and the solution stirred at reflux for 4 hours. Dioxan was removed under reduced pressure and ethyl acetate (5 ml) added. The solution was washed sequentially with 2N hydrochloric acid (2x3 ml) and water (3x3 ml), dried (MgSO₄), evaporated and triturated with isohexane to afford the title compound (107 mg).

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.45 (1H, m), 1.6-1.75 (5H, m), 3.06 (2H, t), 7.25 (1H, t), 7.43 (1H, t), 7.56 (1H, t), 8.56 (1H, t), 8.69 (1H, s), 10.20 (1H, s).

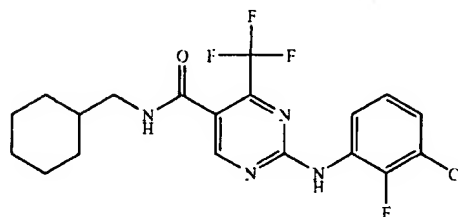
LC/MS, t=3.81 min. Molecular ion observed [MH⁺]=431 consistent with the molecular formula C₁₉H₁₉³⁵ClF₄N₄O.



104

EXAMPLE 167

2-(3-Chloro-2-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



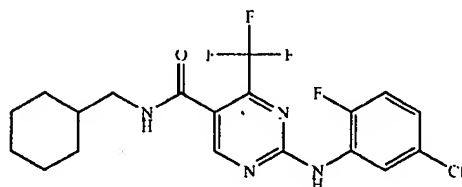
In a manner similar to Example 166(b), 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (100 mg) and 3-chloro-2-fluoroaniline (230 mg, ex Acros) afforded the title compound (101 mg).

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.6-1.8 (5H, m), 3.08 (2H, t), 7.43 (1H, t), 7.67 (1H, m), 8.07 (1H, d), 8.58 (1H, t), 8.80 (1H, s), 10.60 (1H, s).

LC/MS, t=3.71 min. Molecular ion observed [MH⁺]=431 consistent with the molecular formula C₁₉H₁₉³⁵ClF₄N₄O.

EXAMPLE 168

2-(5-Chloro-2-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



In a manner similar to Example 166(b), 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (100 mg) and 5-chloro-2-fluoroaniline (230 mg, ex Avocado) afforded the title compound (116 mg).

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.6-1.75 (5H, m), 3.07 (2H, t), 7.29 (1H, m), 7.36 (1H, t), 7.77 (1H, d of d), 8.57 (1H, t), 8.72 (1H, s), 10.15 (1H, s).

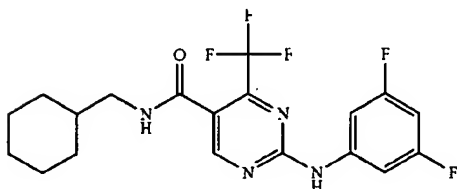
LC/MS, t=3.73 min. Molecular ion observed [MH⁺]=431 consistent with the molecular formula C₁₉H₁₉³⁵ClF₄N₄O.

US 7,635,701 B2

105

EXAMPLE 169

2-(3,5-Difluorophenylamino)-4-trifluoromethyl-5-carboxylic acid cyclohexylmethyl-amide



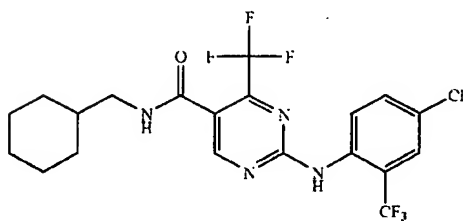
In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (100 mg) and 3,5-difluoroaniline (200 mg, ex Lancaster) afforded the title compound (110 mg).

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.6-1.75 (5H, m), 3.09 (2H, t), 6.89 (1H, t), 7.54 (2H, d), 8.60 (1H, t), 8.85 (1H, s), 10.80 (1H, s)

LC/MS. t=3.74 min, Molecular ion observed [MH⁺]-415 consistent with the molecular formula C₁₉H₁₉F₅N₄O.

EXAMPLE 170

2-(4-Chloro-2-trifluoromethylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (80 mg) and 4-chloro-2-trifluoromethylaniline (107 mg, ex Lancaster) afforded, after purification by mass-directed autoprereparation technique, the title compound (6 mg).

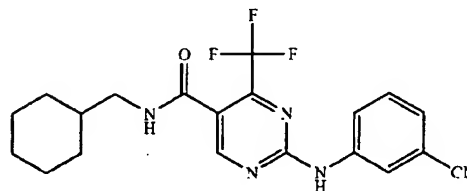
NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.55-1.75 (5H, m), 3.06 (2H, t), 7.76 (1H, d), 7.88 (1H, d), 7.97 (1H, s), 8.56 (1H, t), 8.70 (1H, s), 10.15 (1H, s).

LC/MS. t=3.97 min, Molecular ion observed [MH⁺]=481 consistent with the molecular formula C₂₀H₁₉³⁵ClF₆N₄O.

106

EXAMPLE 171

2-(3-Cyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



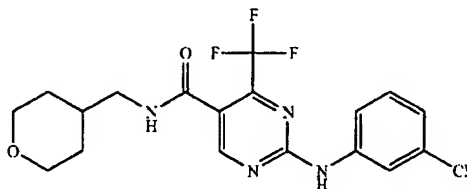
To a solution of 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (50 mg) in acetonitrile (0.5 ml) was added 3-aminobenzonitrile (92 mg, ex Aldrich) and the solution heated at 200° C. under microwave conditions for 45 minutes. Acetonitrile was removed under reduced pressure and ethyl acetate (5 ml) added. The solution was washed sequentially with 2N hydrochloric acid (2×3 ml) and water (3×3 ml), dried (MgSO₄), evaporated and the residue purified using silica gel chromatography with 1:1 ethyl acetate:isohexane to afford the title compound (37 mg).

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.6-1.8 (5H, m), 3.08 (2H, t), 7.50 (1H, d), 7.57 (1H, t), 8.00 (1H, d), 8.25 (1H, s), 8.59 (1H, t), 8.83 (1H, s), 10.75 (1H, s).

LC/MS. t=3.51 min, Molecular ion observed [MH⁺]-404 consistent with the molecular formula C₂₀H₂₀F₃N₅O.

EXAMPLE 172

2-(3-Cyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



In a manner similar to Reference Example 1(c) 2-(3-cyanophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (32 mg) and 4-aminomethyltetrahydropyran (14 mg, ex Combi Blocks) afforded the title compound (26 mg).

NMR (DMSO-d₆) δ 1.15-1.25 (2H, m), 1.62 (2H, d), 1.74 (1H, m), 3.14 (2H, t), 3.27 (2H, t), 3.86 (2H, d of d), 7.50 (1H, d), 7.57 (1H, t), 8.00 (1H, d), 8.26 (1H, s), 8.65 (1H, t), 8.85 (1H, s), 10.70 (1H, s).

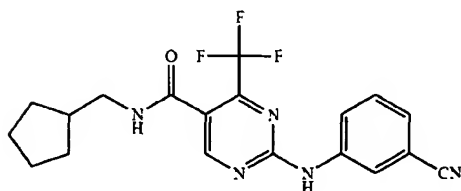
LC/MS. t=2.94 min, Molecular ion observed [MH⁺] 406 consistent with the molecular formula C₁₉H₁₈F₃N₅O₂.

US 7,635,701 B2

107

EXAMPLE 173

2-(3-Cyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-amide



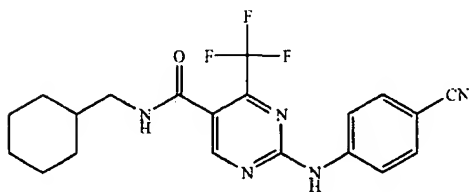
In a manner similar to Reference Example 1(c) 2-(3-cyanophenylamino)-4-trifluoro-methylpyrimidine-5-carboxylic acid (32 mg) and cyclopentanemethanamine hydrochloride (17 mg) afforded the title compound (16 mg).

NMR (DMSO-d₆) δ 1.20-1.30 (2H, m), 1.45-1.6 (4H, m), 1.65-1.75 (2H, m), 2.08 (1H, quintuplet), 3.19 (2H, t), 7.50 (1H, d), 7.57 (1H, t), 8.00 (1H, d), 8.25 (1H, s), 8.63 (1H, t), 8.82 (1H, s), 10.70 (1H, s).

LC/MS, t=3.42 min, Molecular ion observed [MH⁺]=390 consistent with the molecular formula C₁₉H₁₈F₃N₅O

EXAMPLE 174

2-(4-Cyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



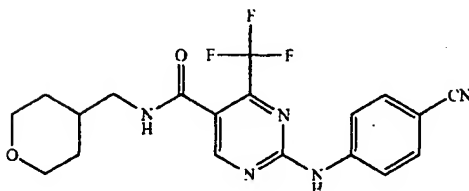
In a manner similar to Reference Example 1(c) 2-(4-cyanophenylamino)-4-trifluoro-methylpyrimidine-5-carboxylic acid (32 mg) and cyclohexanemethanamine (16 μl, ex Lancaster) afforded the title compound (18 mg).

NMR (DMSO-d₆) δ 0.85-1.0 (2H, m), 1.1-1.25 (3H, m), 1.5 (1H, m), 1.6-1.8 (5H, m), 3.08 (2H, t), 7.81 (2H, d), 7.97 (2H, d), 8.61 (1H, t), 8.85 (1H, s), 10.90 (1H, s).

LC/MS, t=3.51 min, Molecular ion observed [MH⁺]=404 consistent with the molecular formula C₂₀H₂₀F₃N₅O.

EXAMPLE 175

2-(4-Cyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



108

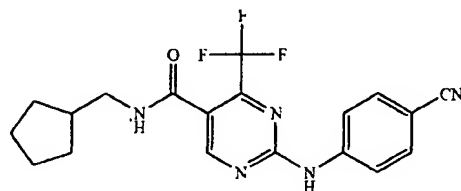
In a manner similar to Reference Example 1(c) 2-(4-cyanophenylamino)-4-trifluoro-methylpyrimidine-5-carboxylic acid (32 mg) and 4-aminomethyltetrahydropyran (14 mg, ex Combi Blocks) afforded the title compound (6 mg).

NMR (DMSO-d₆) δ 1.15-1.25 (2H, m), 1.60 (2H, d), 1.75 (1H, m), 3.14 (2H, t), 3.27 (2H, t), 3.86 (2H, d), 7.82 (2H, d), 7.97 (2H, d), 8.67 (1H, t), 8.87 (1H, s), 10.85 (1H, s).

LC/MS, t=2.92 min, Molecular ion observed [MH⁺]=406 consistent with the molecular formula C₁₉H₁₉F₃N₅O₂.

EXAMPLE 176

2-(4-Cyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-amide



In a manner similar to Reference Example 1(c) 2-(4-cyanophenylamino)-4-trifluoro-methylpyrimidine-5-carboxylic acid (32 mg) and cyclopentanemethanamine hydrochloride (17 mg) afforded the title compound (22.5 mg).

NMR (DMSO-d₆) δ 1.15-1.30 (2H, m), 1.45-1.65 (4H, m), 1.65-1.75 (2H, m), 2.08 (1H, quintuplet), 3.17 (2H, t), 7.82 (2H, d), 7.97 (2H, d), 8.64 (1H, t), 8.84 (1H, s), 10.90 (1H, s).

LC/MS, t=3.40 min, Molecular ion observed [MH⁺]=390 consistent with the molecular formula C₁₉H₁₈F₃N₅O.

EXAMPLE 177

2-(3-Methoxy-5-(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide

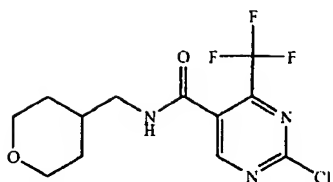
(a). To a solution of 2-chloro-4-trifluoromethyl-pyrimidin-5-carbonyl chloride (1.5 g) in dichloromethane (20 ml) at -20 °C was added a dropwise a solution of 4-aminomethyltetrahydropyran (0.70 g, ex Combi Blocks) and triethylamine (1.05 ml) in dichloromethane (10 ml) and the solution stirred at 0 °C for 1 hour. Dichloromethane was removed under reduced pressure and ethyl acetate (30 ml) added. The solution was washed with 2N hydrochloric acid (3×20 ml), dried (MgSO₄), evaporated and the residue purified using silica gel chromatography with 1:1 ethyl acetate:isohexane to afford 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-yl-methyl)-amide (1.20 g).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.61 (2H, d), 1.74 (1H, m), 3.17 (2H, t), 3.25 (2H, t), 3.86 (2H, d of d), 8.81 (1H, t), 9.20 (1H, s).

LC/MS, t=2.54 min, Molecular ion observed [MH⁺]=324 consistent with the molecular formula C₁₂H₁₃³⁵ClF₃N₃O₂.

US 7,635,701 B2

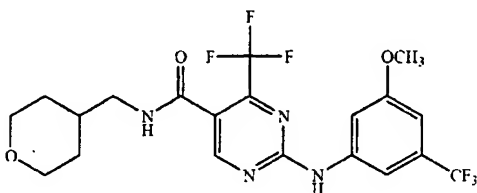
109



(b). In a manner similar to Example 166(b), 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 3-methoxy-5-(trifluoromethyl)aniline (148 mg, ex Aldrich) afforded after stirring at reflux for 24 hours the title compound (51 mg).

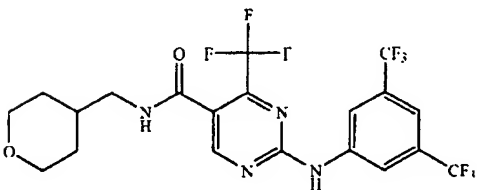
NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.62 (2H, d), 1.74 (1H, m), 3.13 (2H, t), 3.27 (2H, t), 3.83 (3H, s), 3.86 (2H, d), 6.92 (1H, s), 7.73 (1H, s), 7.80 (1H, s), 8.64 (1H, t), 8.85 (1H, s), 10.65 (1H, s).

LC/MS, t_r 3.38 min, Molecular ion observed [MH]⁺=479 consistent with the molecular formula C₂₀H₂₀F₆N₄O₃.



EXAMPLE 178

2-(3,5-Bis-trifluoromethylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid(tetrahydropyran-4-ylmethyl)-amide



In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 3,5-bis(trifluoromethyl)aniline (177 mg, ex Aldrich) afforded, after stirring at reflux for 80 hours and purification by mass-directed autoprereparation technique, the title compound (24.5 mg).

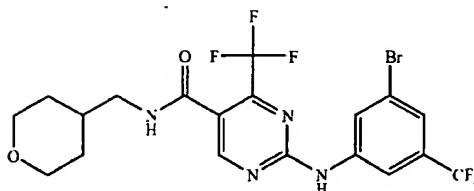
NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.62 (2H, d), 1.75 (1H, m), 3.14 (2H, t), 3.28 (2H, t), 3.86 (2H, d), 7.72 (1H, s), 8.49 (2H, s), 8.67 (1H, t), 8.93 (1H, s), 11.05 (1H, s).

LC/MS, t_r=3.62 min. Molecular ion observed [MH]⁺=517 consistent with the molecular formula C₂₀H₁₇F₉N₄O₂.

110

EXAMPLE 179

2-(3-Bromo-5-(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



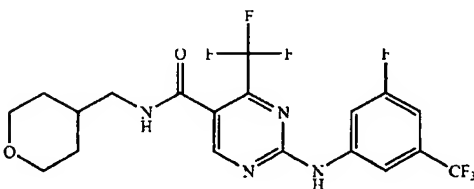
In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 3-bromo-5-(trifluoromethyl)aniline (185 mg, ex Avocado) afforded, after stirring at reflux for 80 hours and purification by mass-directed autoprereparation technique, the title compound (28 mg).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.62 (2H, d), 1.74 (1H, m), 3.14 (2H, t), 3.28 (2H, t), 3.86 (2H, d), 7.60 (1H, s), 8.24 (1H, s), 8.29 (1H, s), 8.66 (1H, t), 8.99 (1H, s), 10.90 (1H, s).

LC/MS, t_r=3.63 min. Molecular ion observed [M-H]⁻=527 consistent with the molecular formula C₁₉H₁₇⁷⁹BrF₆N₄O₂.

EXAMPLE 180

2-(3-Fluoro-5-(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 3-fluoro-5-trifluoromethyl)aniline (138 mg, ex Fluorochem) afforded after stirring at reflux for 24 hours the title compound (44 mg).

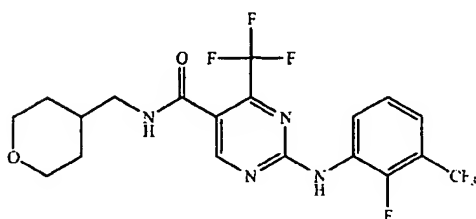
NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.62 (2H, d), 1.75 (1H, m), 3.14 (2H, t), 3.28 (2H, t), 3.86 (2H, d), 7.32 (1H, d), 7.96 (1H, d), 8.06 (1H, s), 8.67 (1H, t), 8.90 (1H, s), 10.90 (1H, s).

LC/MS, t_r=3.45 min. Molecular ion observed [MH]⁺=467 consistent with the molecular formula C₁₉H₁₇F₇N₄O₂.

US 7,635,701 B2

111
EXAMPLE 181

2-(2-Fluoro-3-(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



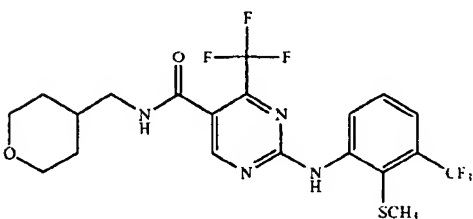
In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 2-fluoro-3-(trifluoromethyl)aniline (138 mg, ex Aldrich) afforded, after stirring at reflux for 80 hours and purification by mass-directed autopreparation technique, the title compound (15 mg).

NMR (DMSO-d₆) δ 1.1-1.25 (2H, m), 1.60 (2H, d), 1.73 (1H, m), 3.11 (2H, t), 3.26 (2H, t), 3.85 (2H, d), 7.43 (1H, t), 7.61 (1H, t), 7.92 (1H, s), 8.63 (1H, t), 8.72 (1H, s), 10.30 (1H, s).

LC/MS, t_r =3.28 min. Molecular ion observed $[MH]^+$ =467 consistent with the molecular formula C₁₉H₁₇F₇N₄O₂.

EXAMPLE 182

2-(2-Methylthio-3-(trifluoromethyl)phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



2-Chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg), 2-methylthio-3-(trifluoromethyl)aniline (125 mg, ex Maybridge) and acetonitrile (0.5 ml) were heated at 190° under microwave irradiation for 30 minutes. The solvent was evaporated in vacuo and the residue purified by mass-directed autopreparation technique, to give the title compound (11 mg).

NMR (DMSO-d₆) δ 1.1-1.25 (2H, m), 1.60 (2H, d), 1.73 (1H, m), 2.24 (3H, s), 3.12 (2H, t), 3.26 (2H, t), 3.85 (2H, d), 7.65 (2H, d), 8.11 (1H, t), 8.64 (1H, t), 8.72 (1H, s), 9.81 (1H, s).

LC/MS, t_r =3.53 min. Molecular ion observed $[MH]^+$ =495 consistent with the molecular formula C₂₀H₂₀F₅N₄O₂S.

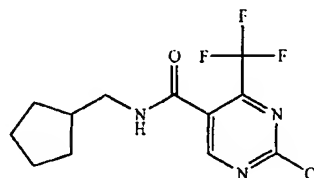
112
EXAMPLE 183

2-(5-Chloro-2-methylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (cyclopentylmethyl)-amide

(a). To a solution of 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxyl chloride (1.0 g, ex Maybridge) in dichloromethane (7 ml) at -2° was added a dropwise a solution of cyclopentanemethanamine hydrochloride (0.55 g) and triethylamine (1.4 ml) in dichloromethane (13 ml) and the solution stirred at 0° for 1 hour. Dichloromethane was removed under reduced pressure and ethyl acetate (20 ml) added. The solution was washed with 2N hydrochloric acid (3x15 ml), dried (MgSO₄), evaporated and triturated with isohexane to afford 2-chloro trifluoromethyl-pyrimidine-5-carboxylic acid (cyclopentylmethyl)-amide (838 mg).

NMR (DMSO-d₆) δ 1.1-1.3 (2H, m), 1.45-1.65 (4H, m), 1.65-1.8 (2H, m), 2.07 (1H, quintuplet), 3.20 (2H, t), 8.78 (1H, t), 9.17 (1H, s).

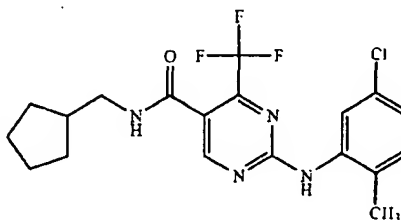
LC/MS, t_r =3.22 min. Molecular ion observed $[M-H]^-$ =306 consistent with the molecular formula C₁₂H₁₃³⁵ClF₃N₃O.



(b) In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethylamide (47.5 mg) and 5-chloro-2-methylaniline (110 mg, ex Aldrich) afforded after stirring at reflux for 30 hours the title compound (41 mg).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.4-1.6 (4H, m), 1.65-1.75 (2H, m), 2.06 (1H, quintuplet), 2.20 (3H, s), 3.14 (2H, t), 7.19 (1H, d), 7.29 (1H, d), 7.48 (1H, s), 8.55 (1H, t), 8.63 (1H, s), 9.83 (1H, s).

LC/MS, t_r =3.68 min. Molecular ion observed $[MH]^+$ =413 consistent with the molecular formula C₁₉H₂₀³⁵ClF₃N₃O.

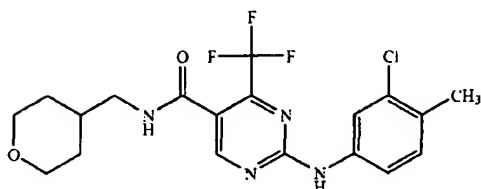


US 7,635,701 B2

113

EXAMPLE 184

2-(3-Chloro-4-methylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



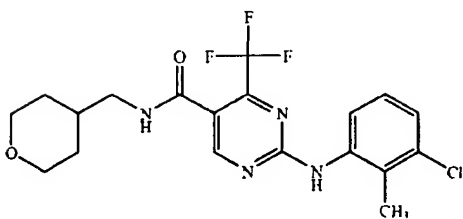
In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 3-chloro-4-methyl-aniline (109 mg) afforded, after stirring at reflux for 24 hours and purification by mass-directed autoprereparation technique, the title compound (35 mg).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.61 (2H, d), 1.74 (1H, m), 2.28 (3H, s), 3.13 (2H, t), 3.27 (2H, t), 3.86 (2H, d of d), 7.31 (1H, d), 7.56 (1H, d), 7.94 (1H, s), 8.61 (1H, t), 8.79 (1H, s), 10.50 (1H, s).

LC/MS. Molecular ion observed [MH⁺]=429 consistent with the molecular formula C₁₉H₂₀³⁵ClF₃N₄O₂

EXAMPLE 185

2-(3-Chloro-2-methylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 3-chloro-2-methyl-aniline (109 mg, known compound CAS No 87-60-5) afforded, after stirring at reflux for 24 hours and purification by mass-directed autoprereparation technique, the title compound (30 mg).

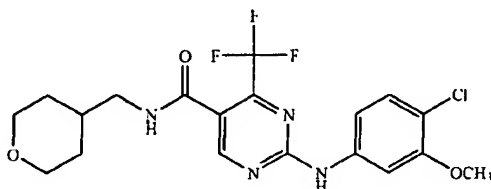
NMR (DMSO-d₆) δ 1.1-1.25 (2H, m), 1.59 (2H, d), 1.72 (1H, m), 2.21 (3H, s), 3.10 (2H, t), 3.26 (2H, t), 3.84 (2H, d of d), 7.24 (1H, t), 7.3 (2H, m), 8.56 (1H, t), 8.61 (1H, s), 9.99 (1H, s)

LC/MS. t=3.19 min. Molecular ion observed [MH⁺]=429 consistent with the molecular formula C₁₉H₂₀³⁵ClF₃N₄O₂.

114

EXAMPLE 186

2-(4-Chloro-3-methoxyphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



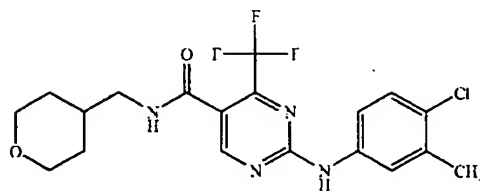
In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 4-chloro-3-methoxy-aniline (122 mg) afforded, after stirring at reflux for 24 hours and purification by mass-directed autoprereparation technique, the title compound (33 mg).

NMR (DMSO-d₆) δ 1.1-1.25 (2H, m), 1.61 (2H, d), 1.73 (1H, m), 3.13 (2H, t), 3.27 (2H, t), 3.83 (3H, s), 3.86 (2H, d), 7.27 (1H, d), 7.37 (1H, d), 7.81 (1H, s), 8.63 (1H, t), 8.80 (1H, s), 10.50 (1H, s).

LC/MS. t=3.26 min. Molecular ion observed [MH⁺]=445 consistent with the molecular formula C₁₉H₂₀³⁵ClF₃N₄O₃.

EXAMPLE 187

2-(4-Chloro-3-methylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide



In a manner similar to Example 166(b) 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide (50 mg) and 4-chloro-3-methyl-aniline (109 mg, ex Lancaster) afforded, after stirring at reflux for 24 hours and purification by mass-directed autoprereparation technique, the title compound (33 mg).

NMR (DMSO-d₆) δ 1.15-1.3 (2H, m), 1.61 (2H, d), 1.73 (1H, m), 2.31 (3H, s), 3.12 (2H, t), 3.27 (2H, t), 3.86 (2H, d), 7.37 (1H, d), 7.62 (1H, d), 7.72 (1H, s), 8.61 (1H, t), 8.77 (1H, s), 10.45 (1H, s).

LC/MS. t=3.41 min. Molecular ion observed [MH⁺]=429 consistent with the molecular formula C₁₉H₂₀³⁵ClF₃N₄O₂

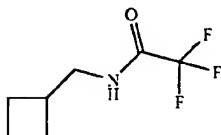
US 7,635,701 B2

115

EXAMPLE 188

2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-methyl-amide

a) N-Cyclobutylmethyl)-2,2,2-trifluoroacetamide



C-cyclobutyl-methylamine hydrochloride (1.82 g) was added to a solution of N,N-diisopropylethylamine (4.14 g) in dry tetrahydrofuran (30 ml) at 0° C. The mixture was stirred at 0° C for 5 mins then cooled to -20° C. A solution of trifluoroacetic anhydride (3.57 g) in tetrahydrofuran (10 ml) was added dropwise over 10 mins and the mixture was then allowed to stir at room temperature for 1 hour. The solution was diluted with ether (100 ml) and water (75 ml), separated and the organic layer washed with water, dilute hydrochloric acid, water and brine, dried (MgSO₄) and evaporated to give the title compound (2.63 g).

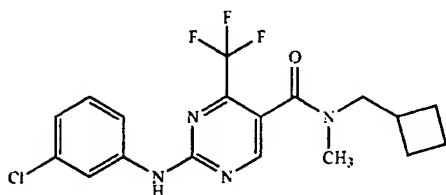
NMR (CDCl₃) δ 1.70 (2H, m excess), 1.93 (2H, m), 2.10 (2H, m), 2.53 (1H, m), 3.39 (2H, t), 6.2 (1H, br s)

b) N-(Cyclobutylmethyl)-N-methylamine

N-Cyclobutylmethyl)-2,2,2-trifluoroacetamide (2.62 g) and iodomethane (3.6 ml) were dissolved in dry acetone (75 ml). Powdered potassium hydroxide (3.2 g) was added and the mixture heated at reflux for 5 mins. The excess iodomethane and acetone were removed under reduced pressure, water (75 ml) added and the solution heated at reflux for 1 hour. The mixture was cooled and ether (75 ml) added. The layers were separated and the organic layer was extracted with dilute hydrochloric acid (75 ml). The aqueous extract was washed with ether, then made strongly basic with sodium hydroxide and extracted with ether (2x75 ml). The extracts were dried (K₂CO₃) and evaporated to give the title compound (517 mg).

NMR (CDCl₃) δ 1.3 (1H, m excess), 1.65 (2H, m), 1.9 (2H, m), 2.05 (2H, m), 2.45 (4H, m), 2.55 (2H, d).

c) 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-methyl-amide



To a solution of N-(cyclobutylmethyl)-N-methylamine (17 mg) in dimethylformamide (1.5 ml) was added successively, 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-

116

carboxylic acid (35 mg), N,N-diisopropylethylamine (38 ul), 1-hydroxybenzotriazole hydrate (23 mg) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (25 mg). The solution was stirred overnight. Dimethylformamide was removed under reduced pressure and ethyl acetate (10 ml) added. The solution was washed sequentially with 10 ml portions of water, saturated sodium bicarbonate solution, water, dilute hydrochloric acid, water and brine, dried (MgSO₄) and evaporated to give the title compound (31 mg).

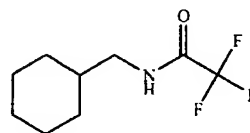
NMR (DMSO-d₆) Rotamers in 60:40 ratio δ 1.5-2.1 (6H, m), 2.50 (0.4H, m-excess), 2.65 (0.6H, m), 2.84 (1.8H, s), 2.94 (1.2H, s), 3.22 (0.4H, d), 3.50 (1.6H, br s), 7.09 (1H, d), 7.36 (1H, m), 7.66 (1H, m), 7.96 (1H, s), 8.76 (1H, d), 10.5 (1H, s).

LC/MS t=3.66 min, Molecular ion observed (MH⁺)=399 consistent with the molecular formula C₁₈H₁₈³⁵ClF₃N₄O

EXAMPLE 189

2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-methyl-amide

a) N-(Cyclohexylmethyl)-2,2,2-trifluoroacetamide



In a manner similar to Example 188a) cyclohexanemethanamine (2.83 g) (Lancaster) gave the title compound (5.09 g).

NMR (CDCl₃) δ 0.95 (2H, m), 1.22 (3H, m), 1.54 (1H, m excess), 1.70 (5H, m), 3.21 (2H, t), 6.3 (1H, br s).

b) N-(Cyclohexylmethyl)-N-methylamine

In a manner similar to Example 188b) N-(cyclohexylmethyl)-2,2,2-trifluoroacetamide (2.98 g) gave the title compound (1.41 g).

NMR (CDCl₃) δ 0.9 (2H, m), 1.23 (4H, m), 1.46 (1H, m excess), 1.72 (5H, m), 2.4 (5H, m).

c) 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-methyl-amide

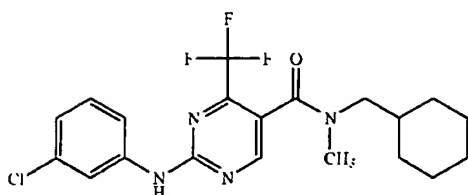
In a manner similar to Example 188c) 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg) and N-(cyclohexylmethyl)-N-methylamine (21 mg) gave the title compound.

NMR (DMSO-d₆) Rotamers in 63:37 ratio δ 0.65-1.30 (5H, m), 1.5-1.8 (6H, m), 2.87 (1.9H, s), 2.97 (1.1H, s), 3.03 (0.7H, d), 3.30 (1.3H, d excess), 7.09 (1H, d), 7.36 (1H, m), 7.66 (1H, d), 7.96 (1H, m), 8.73 (0.37H, s), 8.78 (0.63H, s), 10.6 (1H, s).

LC/MS t=3.87 min, Molecular ion observed (MH⁺)=427 consistent with the molecular formula C₂₀H₂₂¹⁴ClF₃N₄O

US 7,635,701 B2

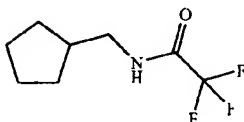
117



EXAMPLE 190

2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-methylamide

a) N-(Cyclopentylmethyl)-2,2,2-trifluoroacetamide



In a manner similar to Example 188a) (cyclopentylmethyl) amine (1.02 g) (Example 2) gave the title compound (1.47 g).

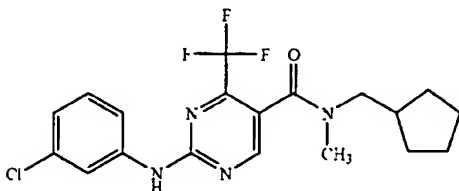
NMR (CDCl₃) δ 1.21 (2H, m), 1.4 (4H, m), 1.78 (2H, m), 2.10 (1H, m), 3.31 (2H, t), 6.3 (1H, br s).

b) N-(Cyclopentylmethyl)-N-methylamine hydrochloride

In a manner similar to Example 188b) N-cyclopentylmethyl-2,2,2-trifluoroacetamide (1.46 g) gave, after treatment with hydrogen chloride in 1,4-dioxan, the title compound (0.77 g).

NMR (D₂O) δ 1.12 (2H, m), 1.5 (4H, m), 1.75 (2H, m), 2.08 (1H, m), 2.61 (3H, s), 2.90 (2H, d)

c) 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-methylamide



In a manner similar to Example 188c) 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg) and N-(cyclopentylmethyl)-N-methylamine hydrochloride (21 mg) together with an additional equivalent of N,N-diisopropylethylamine gave the title compound (42 mg)

NMR (DMSO-d₆) Rotamers in 65:35 ratio δ 1.0-1.8 (8H, m), 2.13 (0.35H, m), 2.27 (0.65H, m), 2.88 (1.95H, s), 2.99

118

(1.05H, s), 3.14 (0.7H, d), 3.41 (1.3H, br s), 7.09 (1H, d), 7.36 (1H, t), 7.66 (1H, d), 7.96 (1H, m), 8.77 (1H, s), 10.6 (1H, s).

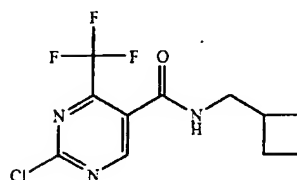
LC/MS t=3.77 min. Molecular ion observed (MH⁺)=413 consistent with the molecular formula C₁₉H₂₀³⁵ClF₃N₄O

EXAMPLE 191

2-(5-Chloro-2-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethylamide

a)

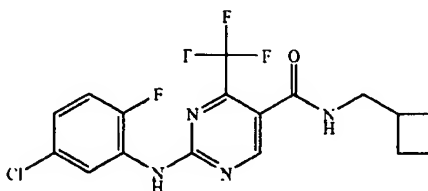
2-Chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethylamide



A mixture of 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (613 mg) (Maybridge) and N-cyclobutylmethylamine hydrochloride (304 mg) in dry dichloromethane (10 ml) was cooled to -30° C and N,N-diisopropylethylamine (958 ul) was added dropwise. The mixture was stirred at room temp for 1 hour. Water (10 ml) was added, the layers separated and the organic layer was washed sequentially with 10 ml portions of water, dilute hydrochloric acid, water, dilute sodium bicarbonate solution and water, dried (MgSO₄) and evaporated. Purification by chromatography on silica gel (dichloromethane/ether 25:1) gave the title compound (449 mg).

NMR (CDCl₃) δ 1.75 (2H, m), 1.93 (2H, m), 2.10 (2H, m), 2.57 (1H, m), 3.50 (2H, t), 5.86 (1H, br s), 8.90 (1H, s).

b) 2-(5-Chloro-2-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethylamide



In a manner similar to Example 166, 5-chloro-2-fluoroaniline (109 mg) (Avocado) and 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethylamide (44 mg) gave the title compound (45 mg).

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 1.99 (2H, m), 2.47 (1H, m excess), 3.25 (2H, t), 7.3 (2H, m), 7.76 (1H, m), 8.56 (1H, t), 8.70 (1H, s), 10.2 (1H, s)

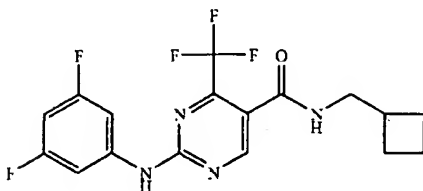
LC/MS t=3.52 min. Molecular ion observed (MH⁺)=403 consistent with the molecular formula C₁₇H₁₅³⁵ClF₃N₄O

US 7,635,701 B2

119

EXAMPLE 192

2-(3,5-Difluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



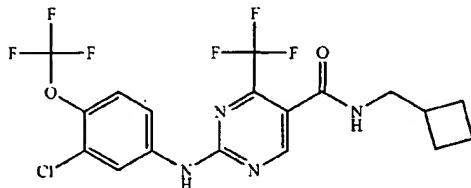
In a manner similar to Example 166, 3,5-difluoroaniline (97 mg) (Lancaster) and 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (44 mg) gave the title compound (46 mg)

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.27 (2H, t), 6.88 (1H, m), 7.55 (2H, m), 8.60 (1H, t), 8.83 (1H, s), 10.8 (1H, s)

LC/MS t=3.54 min. Molecular ion observed (MH⁺)=387 consistent with the molecular formula C₁₇H₁₅F₅N₄O

EXAMPLE 193

2-(3-Chloro-4-trifluoromethoxyphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



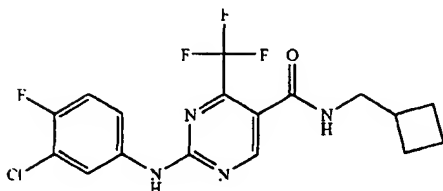
In a manner similar to Example 166, 3-chloro-4-trifluoromethoxy aniline (159 mg) (Lancaster) and 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (44 mg) gave the title compound (59 mg)

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.27 (2H, t), 7.56 (1H, d), 7.76 (1H, m), 8.16 (1H, d), 8.59 (1H, t), 8.81 (1H, s), 10.8 (1H, s)

LC/MS t=3.82 min. Molecular ion observed (MH⁺)=469 consistent with the molecular formula C₁₈H₁₅F₅ClN₄O₂

EXAMPLE 194

2-(3-Chloro-4-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



120

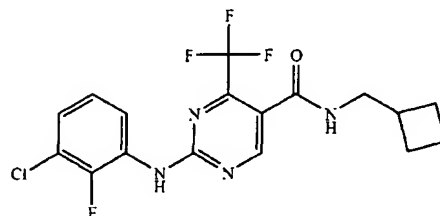
In a manner similar to Example 166, 3-chloro-4-fluoroaniline (109 mg) (Lancaster) and 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (44 mg) gave the title compound (50 mg).

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.27 (2H, t), 7.42 (1H, t), 7.67 (1H, m), 8.04 (1H, m), 8.57 (1H, t), 8.77 (1H, s), 10.6 (1H, s)

LC/MS t=3.60 min. Molecular ion observed (MH⁺)=403 consistent with the molecular formula C₁₇H₁₅³⁵ClF₄N₄O

EXAMPLE 195

2-(3-Chloro-2-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



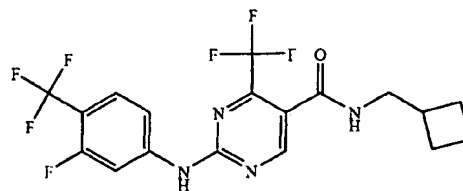
In a manner similar to Example 166, 3-chloro-2-fluoroaniline (109 mg) (Acros) and 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (44 mg) gave the title compound (47 mg).

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.23 (2H, t), 7.22 (1H, t), 7.42 (1H, t), 7.54 (1H, t), 8.55 (1H, t), 8.65 (1H, s), 10.2 (1H, s)

LC/MS t=3.49 min. Molecular ion observed (MH⁺)=403 consistent with the molecular formula C₁₇H₁₅³⁵ClF₄N₄O

EXAMPLE 196

2-(3-Fluoro-4-trifluoromethylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



In a manner similar to Example 166, 3-fluoro-4-trifluoromethylaniline (134 mg) (ABCR) and 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid C-cyclobutylmethyl-amide (44 mg) gave the title compound (41 mg).

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.26 (2H, t), 7.67 (1H, d), 7.75 (1H, t), 8.02 (1H, d), 8.62 (1H, t), 8.87 (1H, s), 11.0 (1H, s)

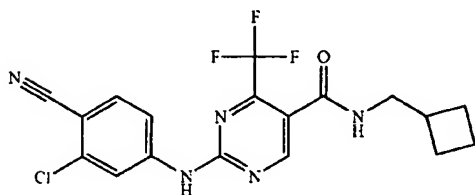
LC/MS t=3.71 min. Molecular ion observed (MH⁺)=437 consistent with the molecular formula C₁₈H₁₅F₅N₄O

US 7,635,701 B2

121

EXAMPLE 197

2-(3-Chloro-4-cyanophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



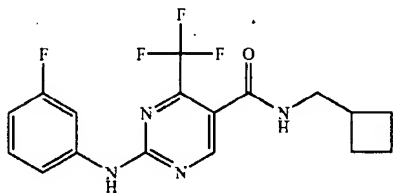
In a manner similar to Example 166, 3-chloro-4-cyananiline (114 mg) (Lancaster) and 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (44 mg) gave the title compound (26 mg)

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.27 (2H, t), 7.83 (1H, m), 7.93 (1H, d), 8.24 (1H, s), 8.62 (1H, t), 8.89 (1H, s), 11.1 (1H, s)

LC/MS t=3.50 min. Molecular ion observed (MH⁺)=410 consistent with the molecular formula C₁₈H₁₅³⁵ClF₃N₅O

EXAMPLE 198

2-(3-Fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



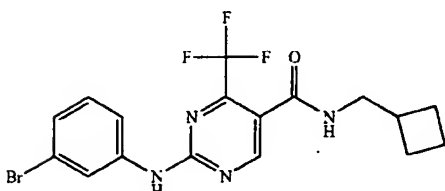
In a manner similar to Example 188, 2-(3-fluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (30 mg) and C-cyclobutylmethylamine hydrochloride (18 mg) gave the title compound (31 mg)

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.26 (2H, t), 6.86 (1H, m), 7.37 (1H, m), 7.50 (1H, d), 7.76 (1H, m), 8.58 (1H, t), 8.78 (1H, s), 10.6 (1H, s)

LC/MS t=3.42 min. Molecular ion observed (MH⁺)=369 consistent with the molecular formula C₁₇H₁₆F₄N₄O

EXAMPLE 199

2-(3-Bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



122

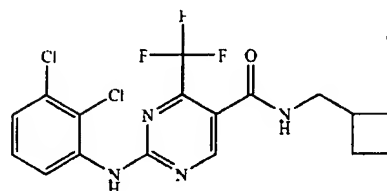
In a manner similar to Example 188, 2-(3-bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and C-cyclobutylmethylamine hydrochloride (18 mg) gave the title compound (33 mg)

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.26 (2H, t), 7.22 (1H, d), 7.31 (1H, t), 7.70 (1H, d), 8.10 (1H, t), 8.57 (1H, t), 8.78 (1H, s), 10.6 (1H, s)

LC/MS t=3.60 min. Molecular ion-observed (MH⁺)=431 consistent with the molecular formula C₁₇H₁₆⁸¹BrF₃N₄O

EXAMPLE 200

2-(2,3-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



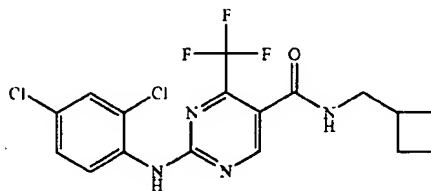
In a manner similar to Example 188, 2-(2,3-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and C-cyclobutylmethylamine hydrochloride (18 mg) gave the title compound (36 mg)

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.24 (2H, t), 7.40 (1H, t), 7.54 (2H, m), 8.54 (1H, t), 8.63 (1H, s), 10.1 (1H, s)

LC/MS t=3.61 min. Molecular ion observed (MH⁺)=419 consistent with the molecular formula C₁₇H₁₅³⁵Cl₂F₃N₄O

EXAMPLE 201

2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



In a manner similar to Example 188, 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and C-cyclobutylmethylamine hydrochloride (18 mg) gave the title compound (37 mg)

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.24 (2H, t), 7.47 (1H, m), 7.58 (1H, d), 7.72 (1H, d), 8.54 (1H, t), 8.65 (1H, s), 10.0 (1H, s)

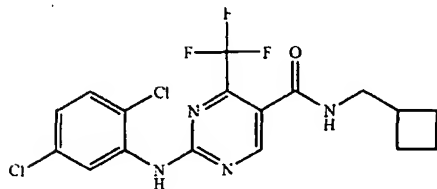
LC/MS t=3.66 min. Molecular ion observed (MH⁺)=419 consistent with the molecular formula C₁₇H₁₅³⁵Cl₂F₃N₄O

US 7,635,701 B2

123

EXAMPLE 202

2-(2,5-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethylamide



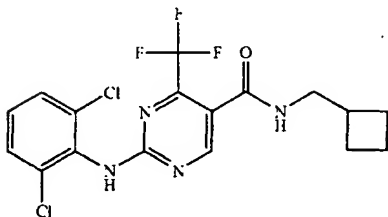
In a manner similar to Example 188, 2-(2,5-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and C-cyclobutylmethylamine hydrochloride (18 mg) gave the title compound (33 mg).

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.24 (2H, t), 7.34 (1H, m), 7.58 (1H, d), 7.72 (1H, d), 8.55 (1H, t), 8.66 (1H, s), 10.0 (1H, s)

LC/MS t=3.65 min, Molecular ion observed (MH⁺)=419 consistent with the molecular formula C₁₇H₁₅³⁵Cl₂F₃N₄O

EXAMPLE 203

2-(2,6-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethylamide



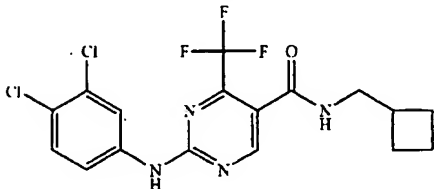
In a manner similar to Example 188, 2-(2,6-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and C-cyclobutylmethylamine hydrochloride (18 mg) gave the title compound (35 mg)

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.22 (2H, t), 7.39 (1H, t), 7.59 (2H, d), 8.56 (2H, m), 10.1 (1H, s).

LC/MS t=3.38 min, Molecular ion observed (MH⁺)=419 consistent with the molecular formula C₁₇H₁₅³⁵Cl₂F₃N₄O

EXAMPLE 204

2-(3,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethylamide



In a manner similar to Example 188, 2-(3,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and C-cyclobutylmethylamine hydrochloride (18 mg) gave the title compound (36 mg).

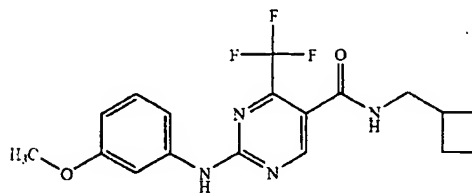
124

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.26 (2H, t), 7.60 (1H, d), 7.69 (1H, m), 8.16 (1H, d), 8.58 (1H, t), 8.80 (1H, s), 10.7 (1H, s)

LC/MS t=3.77 min, Molecular ion observed (MH⁺)=419 consistent with the molecular formula C₁₇H₁₅³⁵Cl₂F₃N₄O

EXAMPLE 205

2-(3-Methoxyphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethylamide



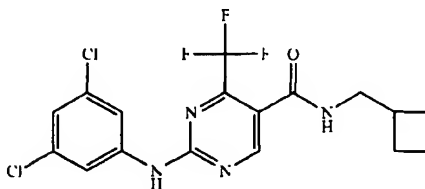
In a manner similar to Example 188, 2-(3-methoxyphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (31 mg) and C-cyclobutylmethylamine hydrochloride (18 mg) gave the title compound (38 mg).

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.26 (2H, t), 3.74 (3H, s), 6.63 (1H, d), 7.24 (2H, m), 7.52 (1H, s), 8.56 (1H, t), 8.72 (1H, s), 10.4 (1H, s)

LC/MS t=3.35 min, Molecular ion observed (MH⁺)=381 consistent with the molecular formula C₁₈H₁₉F₃N₄O₂

EXAMPLE 206

2-(3,5-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethylamide



In a manner similar to Example 188, 2-(3,5-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and C-cyclobutylmethylamine hydrochloride (18 mg) gave the title compound (36 mg).

NMR (DMSO-d₆) δ 1.7 (2H, m), 1.8 (2H, m), 2.0 (2H, m), 2.47 (1H, m excess), 3.26 (2H, t), 7.60 (1H, d), 7.69 (1H, m), 8.16 (1H, d), 8.58 (1H, t), 8.80 (1H, s), 10.7 (1H, s)

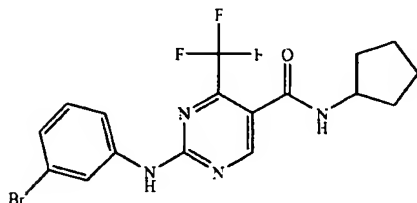
LC/MS t=3.84 min, Molecular ion observed (MH⁺)=419 consistent with the molecular formula C₁₇H₁₅³⁵Cl₂F₃N₄O

US 7,635,701 B2

125

EXAMPLE 207

2-(3-Bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylamide



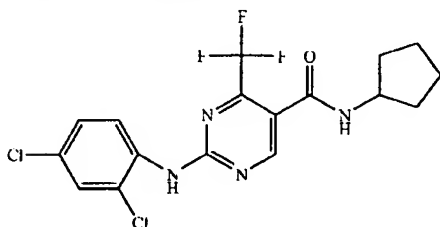
In a manner similar to Example 188, 2-(3-bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (36 mg) and cyclopentylamine (18 mg) gave the title compound (28 mg).

NMR (DMSO-d₆) δ 1.5 (4H, m), 1.66 (2H, m), 1.86 (2H, m), 4.16 (1H, m), 7.22 (1H, d), 7.31 (1H, t), 7.70 (1H, d), 8.10 (1H, t), 8.53 (1H, d), 8.79 (1H, s), 10.6 (1H, s)

LC/MS t=3.39 min. Molecular ion observed (MH⁺)=431 consistent with the molecular formula C₁₇H₁₆⁸¹BrF₃N₄O

EXAMPLE 208

2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylamide



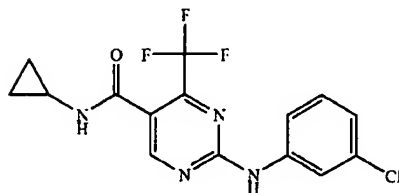
In a manner similar to Example 188, 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (26 mg) and cyclopentylamine (18 mg) gave the title compound (21 mg).

NMR (DMSO-d₆) δ 1.5 (4H, m), 1.63 (2H, m), 1.84 (2H, m), 4.14 (1H, m), 7.47 (1H, m), 7.56 (1H, d), 7.71 (1H, d), 8.50 (1H, d), 8.62 (1H, s), 10.0 (1H, s)

LC/MS t=3.40 min. Molecular ion observed (MH⁺)=419 consistent with the molecular formula C₁₇H₁₅³⁵Cl₂F₃N₄O

EXAMPLE 209

2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopropylamide



In a manner similar to Reference Example 1 (c) 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (35 mg) and cyclopropylamine (9 mg, ex Lancaster) afforded the title compound (32 mg).

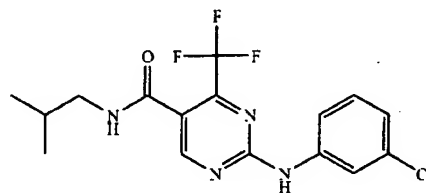
126

NMR (DMSO-d₆) δ 0.49-0.52 (2H, m), 0.69-0.74 (2H, m), 2.78 (1H, m), 7.09 (1H, d), 7.36 (1H, t), 7.65 (1H, d), 7.95 (1H, s), 8.65 (1H, d), 8.80 (1H, s), 10.60 (1H, s)

LC/MS. t=3.25 min. Molecular ion observed (MH⁺)=357 consistent with the molecular formula C₁₅H₁₂N₄OF₃³⁵Cl

EXAMPLE 210

2-(3-Chlorophenylamino)-trifluoromethyl-pyrimidine-5-carboxylic acid (3,3-dimethylbutyl)-amide



In a manner similar to Reference Example 1 (c) 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (50 mg) and 3,3-dimethylbutylamine (17 mg, ex Aldrich) afforded the title compound (32 mg).

NMR (DMSO-d₆) δ 0.96 (6H, d), 1.85 (1H, m), 3.12 (2H, t), 7.16 (1H, d), 7.42 (1H, t), 7.71 (1H, d), 8.02 (1H, s), 8.65 (1H, t), 8.86 (1H, s), 10.70 (1H, s)

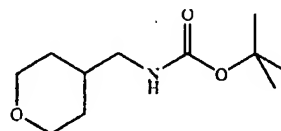
LC/MS. t=3.49 min. Molecular ion observed (MH⁺)=373 consistent with the molecular formula C₁₆H₁₆N₄OF₃³⁵Cl

EXAMPLE 211

2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid methyl-(tetrahydro-pyran-4-ylmethyl)-amide

(a). To a solution of 4-aminomethyltetrahydropyran (500 mg, ex Combi-Blocks, Inc.) in dichloromethane (10 ml) at 0° C. was added triethylamine (1.2 ml) followed by a solution of di-tert-butyl dicarbonate (1.14 g) in dichloromethane (4 ml). The reaction was stirred at 0° C. for 1 h. Dichloromethane was removed under reduced pressure and ethyl acetate added (10 ml). The solution was washed sequentially with 2N hydrochloric acid (10 ml), water (10 ml), 5% sodium bicarbonate solution (10 ml), and water (10 ml), dried (MgSO₄) and evaporated. The residue was purified by chromatography eluting with 2% MeOH/CH₂Cl₂, to afford N-tetrahydro-pyran-4-ylmethylcarbamate (809 mg).

NMR (DMSO-d₆) δ 1.15 (2H, m), 1.45 (9H, s), 1.80-1.95 (3H, d, m), 2.87 (2H, t), 3.30 (2H, t), 3.90 (2H, d, d), 6.95 (1H, t).



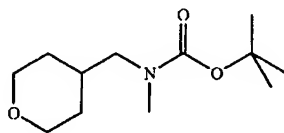
(b). To a solution of N-(tetrahydro-pyran-4-ylmethyl)-carbamate (800 mg) in THF (10 ml) at room temperature under nitrogen was added 60% sodium hydride (164 mg, ex Aldrich) portionwise. The reaction was stirred until effervescence had ceased and then methyl iodide (280 μl, ex Lancaster) was added. Stirring was continued at room

US 7,635,701 B2

127

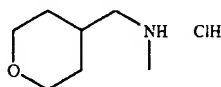
temperature overnight. THF was removed under reduced pressure and ethyl acetate was added (10 ml). This was washed three times with water (10 ml), dried (MgSO_4) and evaporated. The residue was purified by chromatography eluting with 3% $\text{MeOH}/\text{CH}_2\text{Cl}_2$, to afford N-methyl-N-(tetrahydro-pyran-4-ylmethyl)-carbamic acid tert-butyl ester (745 mg).

NMR (DMSO-d_6) δ 1.15 (2H, m), 1.45 (9H, s), 1.50 (2H, m), 1.80 (1H, m), 2.80 (3H, d), 3.08 (2H, d), 3.28 (2H, t), 3.85 (2H, d).



(c). A solution of N-methyl-N-(tetrahydro-pyran-4-ylmethyl)-carbamic acid tert-butyl ester (740 mg) in 4N hydrochloric acid in 1,4-dioxan (10 ml, ex Aldrich) was stirred at room temperature for 1 h. The dioxan was removed under reduced pressure and the residue triturated with ether. The solid was filtered onto a sinter, washed with ether and dried, to afford N-methyl-N-(tetrahydro-pyran-4-ylmethyl)-amine hydrochloride (460 mg).

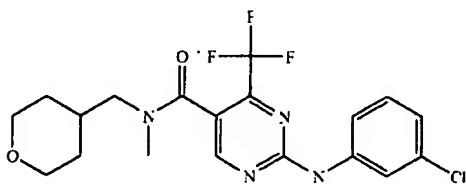
NMR (DMSO-d_6) δ 1.15 (2H, m), 1.65 (2H, d), 1.95 (1H, m), 2.50 (3H, d), 2.80 (2H, d), 3.30 (2H, t), 3.85 (2H, d), 9.0 (2H, s).



(d). In a manner similar to Reference Example 1 (c) 2-(3-chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (50 mg) and N-methyl-N-(tetrahydro-pyran-4-ylmethyl)amine hydrochloride (39 mg) afforded, after Biotage chromatography over silica gel, eluting with 1% $\text{MeOH}/\text{CH}_2\text{Cl}_2$, the title compound (33 mg).

NMR (DMSO-d_6) Rotamers in 65:35 ratio δ 1.05 (0.7H, m), 1.23 (1.3H, m), 1.45 (0.7H, d), 1.58 (1.3H, d), 1.85 (0.35H, m), 2.0 (0.65H, m), 2.89 (1.95H, s), 2.98 (1.05H, s), 3.10-3.40 (4H, m), 3.80 (0.7H, d), 3.88 (1.3H, d), 7.10 (1H, d), 7.36 (1H, t), 7.65 (1H, t), 7.97 (1H, s), 8.75 (0.35H, s), 8.80 (0.65H, s), 10.6 (1H, s).

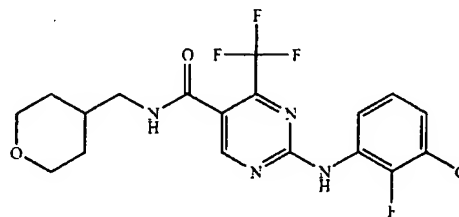
LC/MS, t_r 3.29 min. Molecular ion observed (MH^+)=429 consistent with the molecular formula $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_2\text{F}_3^{35}\text{Cl}$.



128

EXAMPLE 212

2-(2-Fluoro-3-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



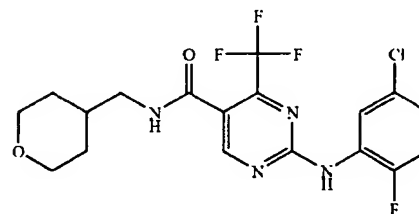
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (100 mg) and 2-fluoro-3-chloroaniline (225 mg, ex Acros) afforded the title compound (85 mg) after purification by trituration with isohexane.

NMR (DMSO-d_6) δ 1.14-1.23 (2H, m), 1.6 (2H, d), 1.72 (1H, m), 3.1 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.24 (1H, t), 7.42 (1H, t), 7.55 (1H, t), 8.61 (1H, t), 8.70 (1H, s), 10.20 (1H, s).

LC/MS, t_r 3.14 min. Molecular ion observed (MH^+)=433 consistent with the molecular formula $\text{C}_{18}\text{H}_{17}\text{N}_4\text{O}_2\text{F}_4^{35}\text{Cl}$.

EXAMPLE 213

2-(2-Fluoro-5-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (100 mg) and 2-fluoro-5-chloroaniline (225 mg, ex Avocado) afforded the title compound (96 mg) after purification by trituration with isohexane.

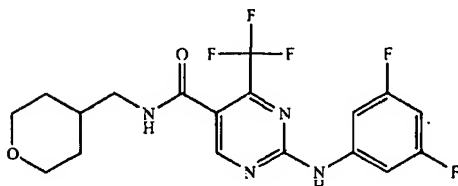
NMR (DMSO-d_6) δ 1.17-1.23 (2H, m), 1.6 (2H, d), 1.71 (1H, m), 3.1 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.27-7.37 (2H, t), 7.76 (1H, dd), 8.62 (1H, t), 8.73 (1H, s), 10.15 (1H, s).

LC/MS, t_r 3.15 min. Molecular ion observed (MH^+)=433 consistent with the molecular formula $\text{C}_{18}\text{H}_{17}\text{N}_4\text{O}_2\text{F}_4^{35}\text{Cl}$.

US 7,635,701 B2

129
EXAMPLE 214

2-(3,5-Difluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



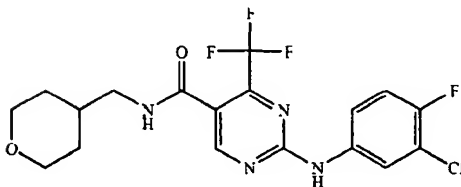
In a manner similar to Example 167, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (100 mg) and 3,5-difluoroaniline (199 mg, ex Lancaster) afforded the title compound (98 mg) after purification by trituration with isohexane.

NMR (DMSO-d₆) δ 1.18-1.23 (2H, m), 1.61 (2H, d), 1.74 (1H, m), 3.13 (2H, t), 3.27 (2H, m), 3.85 (2H, d), 6.88 (1H, t), 7.52-7.55 (2H, m), 8.66 (1H, t), 8.86 (1H, s), 10.80 (1H, s)

LC/MS, t=3.18 min. Molecular ion observed (MH⁺) 417 consistent with the molecular formula C₁₈H₁₇N₄O₂F₅

EXAMPLE 215

2-(4-Fluoro-3-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



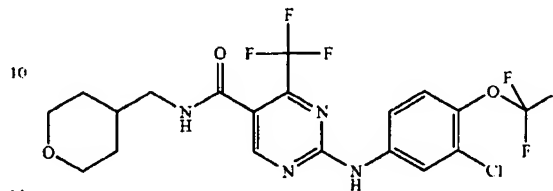
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (100 mg) and 4-fluoro-3-chloroaniline (225 mg, ex Lancaster) afforded the title compound (134 mg) after purification by trituration with isohexane.

NMR (DMSO-d₆) δ 1.18-1.23 (2H, m), 1.61 (2H, d), 1.75 (1H, m), 3.1 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.42 (1H, t), 7.65 (1H, m), 8.05 (1H, dd), 8.63 (1H, t), 8.80 (1H, s), 10.65 (1H, s)

LC/MS, t=3.25 min. Molecular ion observed (MH⁺)=433 consistent with the molecular formula C₁₈H₁₇N₄O₂F₄³⁵Cl

130
EXAMPLE 216

2-(4-Trifluoromethoxy-3-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



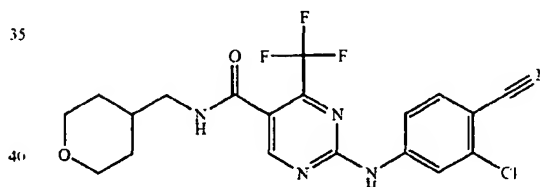
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (100 mg) and 4-trifluoromethoxy-3-chloroaniline (327 mg, ex Lancaster) afforded the title compound (135 mg) after purification by trituration with isohexane.

NMR (DMSO-d₆) δ 1.18-1.23 (2H, m), 1.61 (2H, d), 1.74 (1H, m), 3.13 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.57 (1H, d), 7.75 (1H, dd), 8.14 (1H, d), 8.63 (1H, t), 8.84 (1H, s), 10.74 (1H, s)

LC/MS, t=3.51 min. Molecular ion observed (MH⁺)=499 consistent with the molecular formula C₁₉H₁₇N₄O₃F₆³⁵Cl

EXAMPLE 217

2-(4-Cyano-3-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide

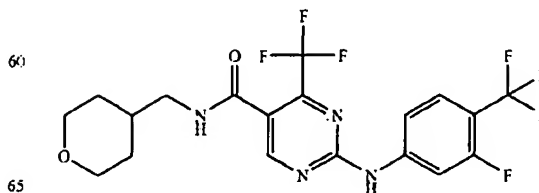


In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (100 mg) and 4-cyano-3-chloroaniline (236 mg, ex Lancaster) afforded the title compound (8 mg). Sample purified by mass directed auto-prep.

LC/MS, t=3.51 min. Molecular ion observed (MH⁺)=440 consistent with the molecular formula C₁₉H₁₇N₅O₂F₃³⁵Cl

EXAMPLE 218

2-(4-Trifluoromethyl-3-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



US 7,635,701 B2

131

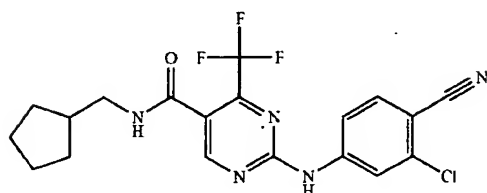
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (100 mg) and 4-trifluoromethyl-3-fluoroaniline (277 mg, ex ABCR) afforded the title compound (125 mg) after purification by trituration with isohexane.

NMR (DMSO-d₆) δ 1.16-1.25 (2H, m), 1.61 (2H, d), 1.73 (1H, m), 3.14 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.67 (1H, d), 7.75 (1H, t), 8.02 (1H, d), 8.68 (1H, t), 8.90 (1H, s), 11.00 (1H, s)

LC/MS, t=3.38 min, Molecular ion observed (MH⁺)=467 consistent with the molecular formula C₁₉H₁₇N₄O₂F₇

EXAMPLE 219

2-(4-Cyano-3-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-amide



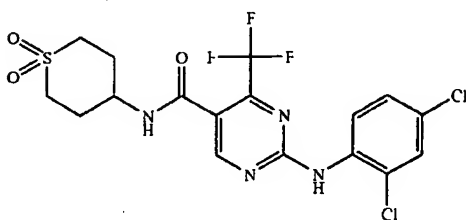
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethylamide (70 mg) and 4-cyano-3-chloroaniline (173 mg, ex Lancaster) afforded the title compound (125 mg). Purified by chromatography eluting with 1:1 ethyl acetate:hexane.

NMR (DMSO-d₆) δ 1.20-1.25 (2H, m), 1.48-1.73 (6H, m), 2.08 (1H, m), 3.18 (2H, t), 7.83 (1H, dd), 7.84 (1H, d), 8.24 (1H, d), 8.66 (1H, t), 8.90 (1H, s), 11.10 (1H, s)

LC/MS, t=3.68 min, Molecular ion observed (MH⁺)=424 consistent with the molecular formula C₁₉H₁₇N₅OF₃Cl

EXAMPLE 220

2-(2,4-Dichloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (1,1-dioxo-hexahydro-11th-thiopyran-4-yl)-amide



In a manner similar to Reference Example 1 (c) 2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (50 mg) and (1,1-dioxo-tetrahydro-2H-thiopyran-4-yl)amine hydrochloride (40 mg) (Ref. WO 02/18380) afforded the title compound (64 mg). Purified by chromatography eluting with 2% MeOH/CH₂Cl₂.

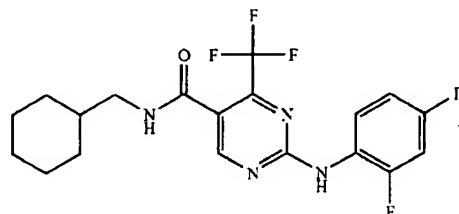
NMR (DMSO-d₆) δ 1.97 (2H, m), 2.13 (2H, m), 3.13 (2H, m), 3.27 (2H, m), 4.10 (1H, m), 7.47 (1H, dd), 7.56 (1H, d), 7.72 (1H, d), 8.67 (1H, t), 8.7 (1H, s), 10.05 (1H, s)

132

LC/MS, t=3.22 min, Molecular ion observed (MH⁺)=483 consistent with the molecular formula C₁₇H₁₅N₄O₃F₃³⁵Cl₂S

EXAMPLE 221

2-(2,4-Difluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



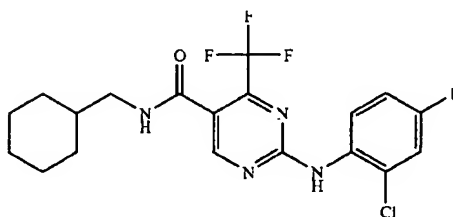
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethylamide (80 mg) and 2,4-difluoroaniline (160 mg, ex Lancaster) afforded the title compound (77 mg) after purification by trituration with isohexane/diethylether.

NMR (DMSO-d₆) δ 0.89-0.95 (2H, m), 1.15-1.20 (3H, m), 1.46-1.47 (1H, m), 1.60-1.72 (5H, m), 3.05 (2H, t), 7.10 (1H, t), 7.35 (1H, m), 7.52 (1H, m), 8.53 (1H, t), 8.62 (1H, s), 10.00 (1H, s)

LC/MS, t=3.63 min, Molecular ion observed (MH⁺)=433 consistent with the molecular formula C₁₉H₁₉N₄OF₅

EXAMPLE 222

2-(2-Chloro-4-fluoro-phenylamino)-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethylamide (80 mg) and 2-chloro-4-fluoroaniline (181 mg, ex Lancaster) afforded the title compound (91 mg).

NMR (DMSO-d₆) δ 0.89-0.95 (2H, m), 1.15-1.20 (3H, m), 1.44-1.46 (1H, m), 1.62-1.72 (5H, m), 3.05 (2H, t), 7.27 (1H, m), 7.55 (2H, m), 8.52 (1H, t), 8.60 (1H, s), 10.00 (1H, s)

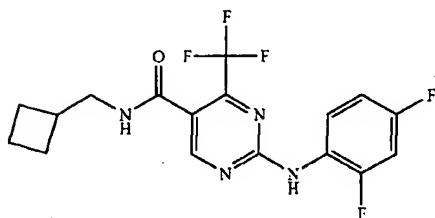
LC/MS, t=3.73 min, Molecular ion observed (MH⁺)=431 consistent with the molecular formula C₁₉H₁₉N₄OF₄³⁵Cl

US 7,635,701 B2

133

EXAMPLE 223

2-(2,4-Difluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



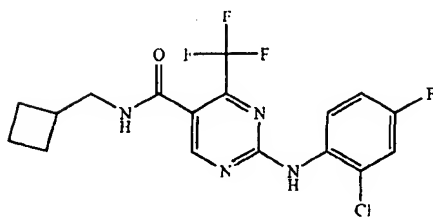
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (80 mg) and 2,4-difluoroaniline (198 mg, ex Lancaster) afforded the title compound (82 mg) after purification by trituration with isohexane/diethylether.

NMR (DMSO-d₆) δ 1.67-2.01 (6H, m), 2.47 (1H, m), 3.23 (2H, t), 7.10 (1H, t), 7.35 (1H, m), 7.52 (1H, m), 8.53 (1H, t), 8.62 (1H, s), 10.00 (1H, s)

LC/MS, t=3.40 min Molecular ion observed (MH⁺)=386 consistent with the molecular formula C₁₇H₁₅N₄OF₅

EXAMPLE 224

2-(2-Chloro-4-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (80 mg) and 2-chloro-4-fluoroaniline (198 mg, ex Lancaster) afforded the title compound (80 mg) after purification by trituration with 2N hydrochloric acid.

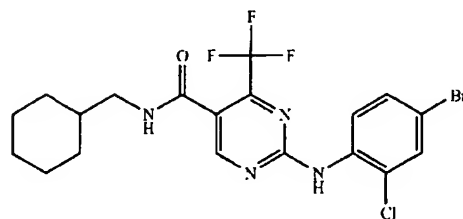
NMR (DMSO-d₆) δ 1.67-2.00 (6H, m), 2.46 (1H, m), 3.23 (2H, t), 7.27 (1H, m), 7.55 (2H, m), 8.52 (1H, t), 8.58 (1H, s), 9.90 (1H, s)

LC/MS, t=3.51 min, Molecular ion observed (MH⁺)=403 consistent with the molecular formula C₁₇H₁₅N₄OF₄³⁵Cl

134

EXAMPLE 225

2-(2-Chloro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



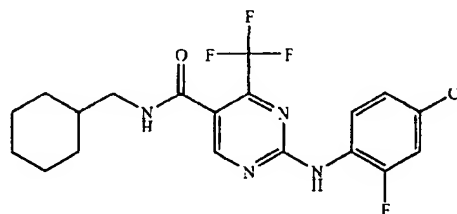
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (80 mg) and 2-chloro-4-bromoaniline (257 mg, ex Lancaster) afforded the title compound (96 mg) after purification by trituration with 2N hydrochloric acid.

NMR (DMSO-d₆) δ 0.89-0.95 (2H, m), 1.15-1.20 (3H, m), 1.44-1.46 (1H, m), 1.62-1.72 (5H, m), 3.05 (2H, t), 7.52 (1H, d), 7.58 (1H, dd), 7.82 (1H, d), 8.55 (1H, t), 8.63 (1H, s), 10.00 (1H, s)

LC/MS, t=3.97 min. Molecular ion observed (MH⁺)=493 consistent with the molecular formula C₁₉H₁₉N₄OF₃³⁵Cl⁸¹Br

EXAMPLE 226

2-(2-Fluoro-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (80 mg) and 2-fluoro-4-chloroaniline (180 mg, ex Lancaster) afforded the title compound (73 mg) after purification by trituration with 2N hydrochloric acid.

NMR (DMSO-d₆) δ 0.95-0.98 (2H, m), 1.15-1.20 (3H, m), 1.44-1.46 (1H, m), 1.66-1.72 (5H, m), 3.05 (2H, t), 7.31 (1H, d), 7.53 (1H, dd), 7.60 (1H, t), 8.55 (1H, t), 8.66 (1H, s), 10.00 (1H, s)

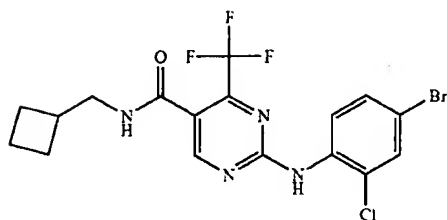
LC/MS, t=3.79 min, Molecular ion observed (MH⁺)=431 consistent with the molecular formula C₁₉H₁₉N₄OF₄³⁵Cl

US 7,635,701 B2

135

EXAMPLE 227

2-(2-Chloro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



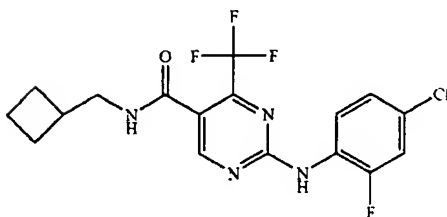
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (80 mg) and 2-chloro-4-bromoaniline (281 mg, ex Lancaster) afforded the title compound (103 mg) after purification by trituration with 2N hydrochloric acid.

NMR (DMSO-d₆) δ 1.67-2.00 (6H, m), 2.45 (1H, m), 3.23 (2H, t), 7.50 (1H, d), 7.58 (1H, dd), 7.82 (1H, d), 8.53 (1H, t), 8.61 (1H, s), 10.00 (1H, s)

LC/MS. t=3.77 min. Molecular ion observed (MH⁺)=465 consistent with the molecular formula C₁₇H₁₅N₄OF₃³⁵Cl⁸¹Br

EXAMPLE 228

2-(2-Fluoro-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (80 mg) and 2-fluoro-4-chloroaniline (198 mg, ex Lancaster) afforded the title compound (94 mg) after purification by trituration with 2N hydrochloric acid.

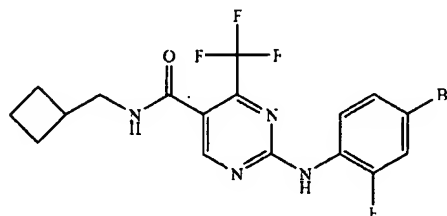
NMR (DMSO-d₆) δ 1.67-2.08 (6H, m), 2.45 (1H, m), 3.23 (2H, t), 7.31 (1H, d), 7.53 (1H, dd), 7.60 (1H, t), 8.53 (1H, t), 8.64 (1H, s), 10.00 (1H, s)

LC/MS. t=3.59 min. Molecular ion observed (MH⁺)=403 consistent with the molecular formula C₁₇H₁₅N₄O F₄³⁵Cl⁸¹

136

EXAMPLE 229

2-(2-Fluoro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



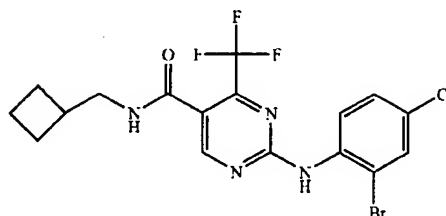
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (80 mg) and 2-fluoro-4-bromoaniline (259 mg, ex Lancaster) afforded the title compound (95 mg) after purification by trituration with 2N hydrochloric acid.

NMR (DMSO-d₆) δ 1.67-2.00 (6H, m), 2.45 (1H, m), 3.23 (2H, t), 7.43 (1H, d), 7.54 (1H, t), 7.63 (1H, dd), 8.53 (1H, t), 8.64 (1H, s), 10.00 (1H, s)

LC/MS. t=3.63 min. Molecular ion observed (MH⁺)=449 consistent with the molecular formula C₁₇H₁₅N₄OF₄⁸¹Br

EXAMPLE 230

2-(2-Bromo-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (80 mg) and 2-bromo-4-chloroaniline (281 mg, ex Lancaster) afforded the title compound (105 mg) after purification by trituration with 2N hydrochloric acid.

NMR (DMSO-d₆) δ 1.67-2.08 (6H, m), 2.45 (1H, m), 3.23 (2H, t), 7.52 (2H, m), 7.85 (1H, s), 8.53 (1H, t), 8.60 (1H, s), 10.00 (1H, s)

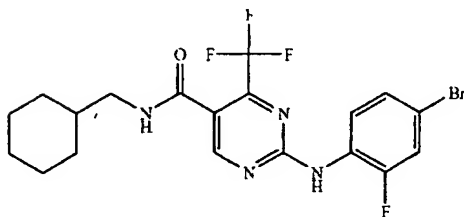
LC/MS. t=3.75 min. Molecular ion observed (MH⁺)=465 consistent with the molecular formula C₁₇H₁₅N₄OF₃³⁵Cl⁸¹Br

US 7,635,701 B2

137

EXAMPLE 231

2-(2-Fluoro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



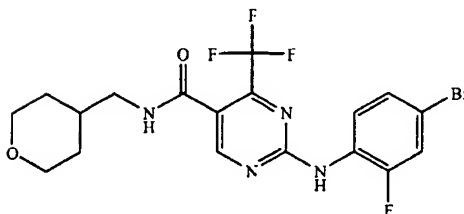
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (80 mg) and 2-fluoro-4-bromoaniline (236 mg, ex Lancaster) afforded the title compound (96 mg) after purification by titration with 2N hydrochloric acid.

NMR (DMSO-d₆) δ 0.90-0.92 (2H, m), 1.15-1.20 (3H, m), 1.44-1.46 (1H, m), 1.63-1.72 (5H, m), 3.05 (2H, t), 7.44 (1H, d), 7.55 (1H, t), 7.64 (1H, dd), 8.55 (1H, t), 8.66 (1H, s), 10.00 (1H, s)

LC/MS, t 3.83 min, Molecular ion observed (MH⁺) 477 consistent with the molecular formula C₁₉H₁₉N₄O₂F₄⁸¹Br

EXAMPLE 232

2-(2-Fluoro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (80 mg) and 2-fluoro-4-bromoaniline (235 mg, ex Lancaster) afforded the title compound (100 mg) after purification by titration with 2N hydrochloric acid.

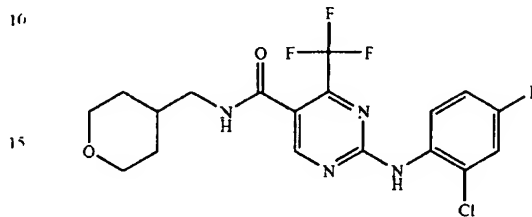
NMR (DMSO-d₆) δ 1.16-1.23 (2H, m), 1.60 (2H, d), 1.71 (1H, m), 3.1 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.43 (1H, d), 7.55 (1H, t), 7.64 (1H, dd), 8.60 (1H, t), 8.65 (1H, s), 10.10 (1H, s)

LC/MS, t=3.28 min, Molecular ion observed (MH⁺)=479 consistent with the molecular formula C₁₈H₁₇N₄O₂F₄⁸¹Br

138

EXAMPLE 233

2-(2-Chloro-4-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



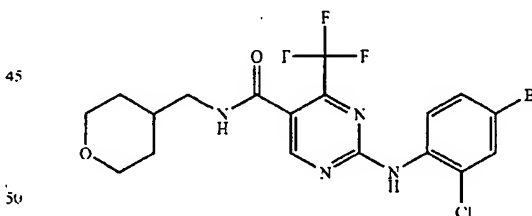
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (80 mg) and 2-chloro-4-fluoroaniline (180 mg, ex Lancaster) afforded the title compound (95 mg) after purification by titration with 2N hydrochloric acid.

NMR (DMSO-d₆) δ 1.14-1.23 (2H, m), 1.59 (2H, d), 1.71 (1H, m), 3.1 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.27 (1H, m), 7.55 (2H, m), 8.58 (1H, t), 8.61 (1H, s), 10.00 (1H, s)

LC/MS, t=3.14 min, Molecular ion observed (MH⁺)=433 consistent with the molecular formula C₁₈H₁₇N₄O₂F₄³⁵Cl

EXAMPLE 234

2-(2-Chloro-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (80 mg) and 2-chloro-4-bromoaniline (255 mg, ex Lancaster) afforded the title compound (102 mg) after purification by titration with 2N hydrochloric acid.

NMR (DMSO-d₆) δ 1.14-1.23 (2H, m), 1.58 (2H, d), 1.72 (1H, m), 3.1 (2H, t), 3.28 (2H, m), 3.84 (2H, d), 7.51 (1H, d), 7.59 (1H, dd), 7.82 (1H, d), 8.58 (1H, t), 8.63 (1H, s), 10.00 (1H, s)

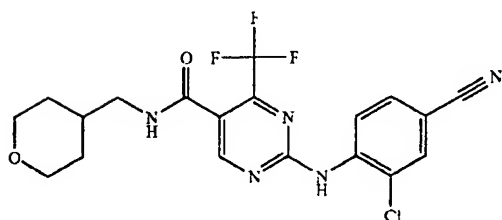
LC/MS, t=3.42 min, Molecular ion observed (MH⁺)=495 consistent with the molecular formula C₁₈H₁₇N₄O₂F₃⁸¹Cl⁸¹Br

US 7,635,701 B2

139

EXAMPLE 235

2-(2-Chloro-4-cyano-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid(tetrahydro-pyran-4-ylmethyl)-amide



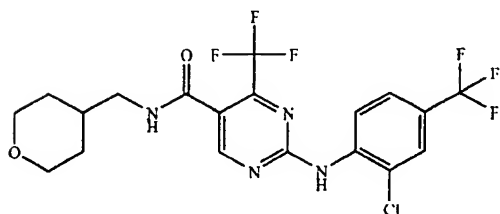
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (80 mg) and 2-chloro-4-cyanoaniline (188 mg, ex Lancaster) afforded the title compound (22 mg). Sample purified by mass directed auto-prep.

NMR (DMSO-d₆) δ 1.14-1.23 (2H, m), 1.59 (2H, d), 1.72 (1H, m), 3.12 (2H, t), 3.23 (2H, m), 3.85 (2H, d), 7.87 (1H, d), 7.92 (1H, d), 8.14 (1H, s), 8.65 (1H, t), 8.75 (1H, s), 10.20 (1H, s)

LC/MS, t=3.11 min. Molecular ion observed (MH⁺)=440 consistent with the molecular formula C₁₉H₁₇N₅O₂F₃³⁵Cl

EXAMPLE 236

2-(2-Chloro-4-trifluoromethyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (80 mg) and 2-chloro-4-trifluoromethylaniline (241 mg, ex Lancaster) afforded the title compound (48 mg). Sample purified by mass directed auto-prep.

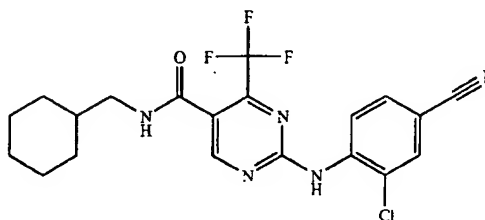
NMR (DMSO-d₆) δ 1.17-1.23 (2H, m), 1.59 (2H, d), 1.72 (1H, m), 3.12 (2H, t), 3.23 (2H, m), 3.85 (2H, d), 7.77 (1H, d), 7.88 (1H, d), 7.96 (1H, s), 8.63 (1H, t), 8.72 (1H, s), 10.15 (1H, s)

LC/MS, t=3.47 min. Molecular ion observed (MH⁺)=483 consistent with the molecular formula C₁₉H₁₇N₄O₂F₆³⁵Cl

140

EXAMPLE 237

2-(2-Chloro-4-cyano-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



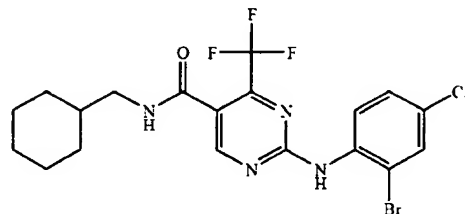
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (80 mg) and 2-chloro-4-cyanoaniline (189 mg, ex Lancaster) afforded the title compound (15 mg). Sample purified by mass directed auto-prep.

NMR (DMSO-d₆) δ 0.90 (2H, m), 1.15-1.23 (3H, m), 1.44-1.46 (1H, m), 1.67-1.73 (5H, m), 3.06 (2H, t), 7.87 (1H, dd), 7.92 (1H, d), 8.14 (1H, d), 8.58 (1H, t), 8.74 (1H, s), 10.10 (1H, s)

LC/MS, t=3.67 min. Molecular ion observed (MH⁺)=438 consistent with the molecular formula C₂₀H₁₉N₅O₂F₃³⁵Cl

EXAMPLE 238

2-(2-Bromo-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (80 mg) and 2-bromo-4-chloroaniline (257 mg, ex Lancaster) afforded the title compound (23 mg). Sample purified by mass directed auto-prep.

NMR (DMSO-d₆) δ 0.89-0.95 (2H, m), 1.15-1.20 (3H, m), 1.44-1.46 (1H, m), 1.62-1.72 (5H, m), 3.04 (2H, t), 7.52 (2H, m), 7.85 (1H, d), 8.53 (1H, t), 8.61 (1H, s), 10.00 (1H, s)

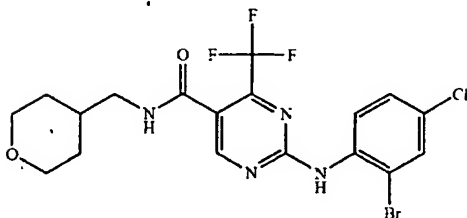
LC/MS, t=3.94 min. Molecular ion observed (MH⁺)=493 consistent with the molecular formula C₁₉H₁₉N₄O₂F₃³⁵Cl⁸¹Br

US 7,635,701 B2

141

EXAMPLE 239

2-(2-Bromo-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



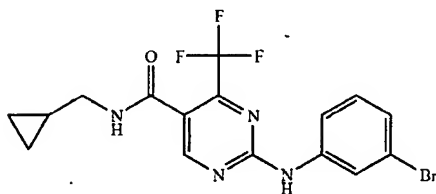
In a manner similar to Example 166, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (80 mg) and 2-bromo-4-chloroaniline (255 mg, ex Lancaster) afforded the title compound (6 mg). Sample purified by mass directed auto-prep.

NMR (DMSO-d₆) δ 1.14-1.23 (2H, m), 1.58 (2H, d), 1.72 (1H, m), 3.1 (2H, t), 3.28 (2H, m), 3.84 (2H, d), 7.50 (2H, m), 7.82 (1H, d), 8.58 (1H, t), 8.63 (1H, s), 10.00 (1H, s)

LC/MS, t=3.40 min. Molecular ion observed (MH⁺)=495 consistent with the molecular formula C₁₈H₁₇N₄O₂F₃³⁵Cl⁸¹Br

EXAMPLE 240

2-(3-Bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopropylmethyl-amide



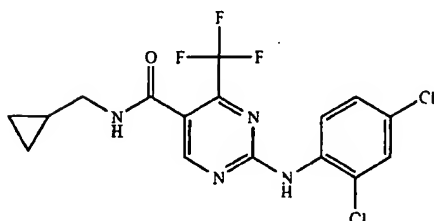
In a manner similar to Reference Example 1 (c) 2-(3-bromophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (80 mg) and cyclopropylmethylamine (19 mg, ex Lancaster) afforded the title compound (24 mg). Sample purified by mass directed auto-prep.

NMR (DMSO-d₆) δ 0.22 (2H, m), 0.45 (2H, m), 1.67 (1H, m), 3.13 (2H, t), 7.23 (1H, d), 7.30 (1H, t), 7.72 (1H, d), 8.10 (1H, m), 8.68 (1H, t), 8.80 (1H, s), 10.60 (1H, s)

LC/MS, t=3.49 min. Molecular ion observed (MH⁺)=417 consistent with the molecular formula C₁₆H₁₄N₄OF₃⁸¹Br

EXAMPLE 241

2-(2,4-Dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopropylmethyl-amide



142

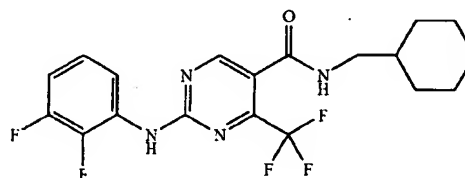
In a manner similar to Reference Example 1 (c) 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (80 mg) and cyclopropylmethylamine (19 mg, ex Lancaster) afforded the title compound (58 mg).

NMR (DMSO-d₆) δ 0.22 (2H, m), 0.45 (2H, m), 1.67 (1H, m), 3.13 (2H, t), 7.23 (1H, d), 7.30 (1H, t), 7.72 (1H, d), 8.10 (1H, m), 8.68 (1H, t), 8.80 (1H, s), 10.60 (1H, s)

LC/MS, t=3.56 min. Molecular ion observed (MH⁺)=405 consistent with the molecular formula C₁₆H₁₃N₄OF₃³⁵Cl

EXAMPLE 242

2-(2,3-Difluorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



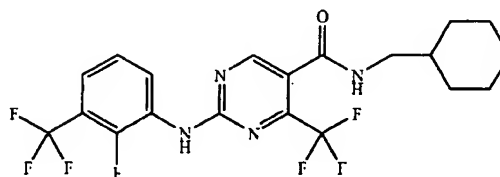
To a solution of 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (Example 166a) (50 mg) in 1,4-dioxan (1 ml) was added 2,3-difluoroaniline (Aldrich) (113 mg) and the mixture was stirred at reflux for 47 hours using a Radleys Greenhouse Parallel Synthesiser. The dioxan was removed using a nitrogen blow down unit. The residue was taken up into methanol (0.5 ml) and dimethylsulfoxide (0.5 ml) and purified using a mass directed auto-preparative system to give the title compound (16 mg)

NMR (Chloroform-d₆) δ 0.94-1.08 (2H, m), 1.15-1.34 (3H, m), 1.5-1.6 (>1H, m & water), 1.65-1.73 (1H, m), 1.73-1.83 (4H, m), 3.30 (2H, t), 5.91 (1H, bs), 6.88-6.98 (1H, m), 7.08-7.1 (1H, m), 7.66 (1H, bs), 8.16-8.25 (1H, m), 8.75 (1H, s).

LC/MS t=3.66 min, [MH⁺] 415 consistent with the molecular formula C₁₉H₁₉F₄N₄O

EXAMPLE 243

2-(2-Fluoro-3-trifluoromethyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



In a manner similar to Example 242, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (Example 166a) (50 mg) in 1,4-dioxan (1 ml) and 2-fluoro-3-trifluoromethylphenylamine (Aldrich) (156 mg) were reacted to give the title compound (11 mg)

NMR (Chloroform-d₆) δ 0.94-1.08 (2H, m), 1.15-1.34 (3H, m), 1.55-1.59 (1H, m), 1.65-1.73 (1H, m), 1.73-1.83 (4H, m), 3.30 (2H, t), 5.91 (1H, bs), 7.28-7.37 (2H, m), 7.74 (1H, bs), 8.65-8.73 (1H, m), 8.77-8.80 (1H, m)

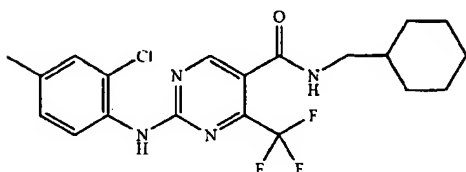
US 7,635,701 B2

143

LC/MS $t=3.66$ min $[MH^+]=465$ consistent with the molecular formula $C_{20}H_{19}F_7N_4O$

EXAMPLE 244

2-(2-Chloro-4-methylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



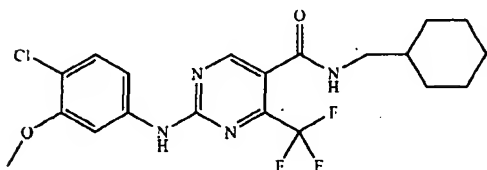
To a solution of 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (Example 166a) (50 mg) in 1,4-dioxan (1 ml) was added 2-chloro-4-methylphenylamine (Aldrich) (109 mg) the mixture was stirred at reflux for 24 hours using a Radleys Greenhouse Parallel Synthesiser. The dioxan was removed using a nitrogen blow down unit. The residue was taken up into methanol (0.5 ml) and dimethylsulfoxide (0.5 ml) and purified using mass directed auto-preparative system to give the title compound (24 mg).

NMR (Methanol- d_6) δ 1.50-1.60 (2H, m), 1.70-1.89 (3H, m), 2.06-2.15 (1H, m), 2.2-2.26 (1H, m), 2.27-2.38 (4H, m), 2.88 (3H, s), 3.71 (2H, d), 7.68 (1H, d), 7.85 (1H, s), 8.31 (1H, d), 9.10 (1H, s).

LC/MS $t=3.81$ min, $[MH^+]=427$ consistent with the molecular formula $C_{20}H_{22}^{35}ClF_3N_4O$

EXAMPLE 245

2-(4-Chloro-3-methoxyphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



In a manner similar to Example 243, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (Example 166a) (50 mg) in 1,4-dioxan (1 ml) and 4-chloro-3-methoxy-phenylamine (Wychem) (122 mg) were reacted to give the title compound (33 mg).

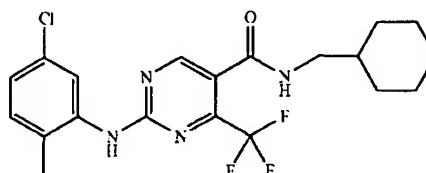
NMR (Methanol- d_6) δ 0.95-1.06 (2H, m), 1.20-1.34 (3H, m), 1.55-1.64 (1H, m), 1.65-1.71 (1H, m), 1.72-1.85 (4H, m), 3.19 (2H, d), 3.90 (3H, s), 7.18 (1H, dd), 7.27 (1H, d), 7.80 (1H, bs), 8.64 (1H, s).

LC/MS $t=3.79$ min, $[MH^+]=443$ consistent with the molecular formula $C_{20}H_{22}^{15}ClF_3N_4O_2$

144

EXAMPLE 246

2-(5-Chloro-2-methylphenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide



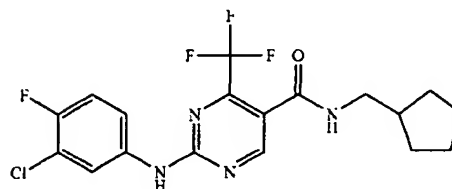
In a manner similar to Example 243, 2-chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclohexylmethyl-amide (Example 166a) (50 mg) in 1,4-dioxan (1 ml) and 5-chloro-2-methyl aniline (Aldrich) (110 mg) were reacted to give the title compound (36 mg).

NMR (Methanol- d_6) δ 1.47-1.59 (2H, m), 1.72-1.89 (3H, m), 2.05-2.18 (1H, m), 2.19-2.25 (1H, m), 2.31 (4H, t), 2.79 (3H, s), 3.71 (2H, d), 7.76 (1H, dd), 7.76 (1H, d), 8.17 (1H, d), 9.09 (1H, s).

LC/MS $t=3.77$ min $[MH^+]=427$ consistent with the molecular formula $C_{20}H_{22}^{35}ClF_3N_4O$

EXAMPLE 247

2-(3-Chloro-4-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-amide



2-Chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-amide (116 mg Example 183a), 3-chloro-4-fluoroaniline (ex-Aldrich, 275 mg), and 1,4-dioxan (1.2 ml) were stirred at 100° C. under nitrogen for 6 h. The cooled reaction mixture was evaporated in vacuo, treated with ethyl acetate (5 ml), washed with aqueous 2M hydrochloric acid (2x3 ml), followed by brine, and dried (Na_2SO_4). The solution was evaporated in vacuo to give the title compound (104 mg).

NMR ($DMSO-d_6$) δ 1.5-1.32 (2H, m), 1.46-1.66 (4H, m), 1.66-1.78 (2H, m), 2.1 (1H, q), 3.17 (2H, t), 7.4 (1H, t), 7.63-7.7 (1H, m), 8.05 (1H, dd), 8.61 (1H, t), 8.79 (1H, s), 10.6 (1H, s).

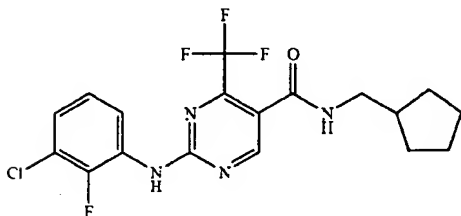
LC/MS $t=3.7$ min. Molecular ion observed $[MH^+]=417$ consistent with the molecular formula $C_{18}H_{11}F_4N_4O$.

US 7,635,701 B2

145

EXAMPLE 248

2-(3-Chloro-2-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-amide



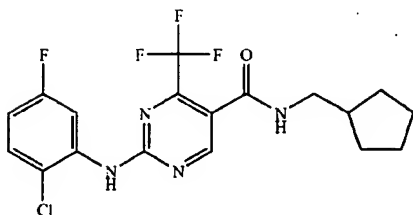
In a manner similar to Example 247, 3-chloro-2-fluoroaniline (ex-Acros, 275 mg) was reacted for 18 h, worked up analogously, then stirred in isohexane (6 ml), and filtered off to give the title compound (82 mg).

NMR δ (CDCl₃) 1.2-1.34 (2H, m), 1.55-1.76 (>4H, m+H₂O), 1.78-1.89 (2H, m), 2.16 (1H, q), 3.41 (1H, t), 5.83-5.95 (1H, brt), 7.1-7.18 (2H, m), 7.28 (1H, s), 7.66 (1H, brs), 8.3-8.4 (1H, m), 8.75 (1H, s)

LC/MS t_r 3.7 min, Molecular ion observed [MH⁺] 417 consistent with the molecular formula C₁₈H₁₇ClF₄N₄O

EXAMPLE 249

2-(2-Chloro-5-fluoro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-amide



2-Chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-amide (100 mg Example 183a), 2-chloro-5-fluoroaniline (ex-Fluorochem, 237 mg), and 1,4-dioxan (1 ml) were stirred at 100°C under nitrogen for 18 h. The cooled reaction mixture was evaporated in vacuo, treated with ethyl acetate (5 ml), washed with aqueous 2M hydrochloric acid (2x3 ml), followed by water (2x3 ml), and dried (Na₂SO₄). The solution was evaporated in vacuo and the residue purified by mass directed auto-preparative purification to give the title compound (35 mg).

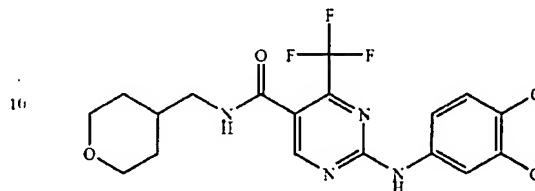
NMR δ (CDCl₃) 1.2-1.35 (2H, m), 1.53-1.76 (>4H, m+H₂O), 1.78-1.90 (2H, m), 2.17 (1H, q), 3.41 (2H, dd), 5.9 (1H, brt), 7.0-7.11 (2H, m), 7.65-7.7 (1H, m), 8.56 (1H, dd), 8.79 (1H, s).

LC/MS t_r 3.67 min, Molecular ion observed [MH⁺] 417 consistent with the molecular formula C₁₈H₁₇ClF₄N₄O.

146

EXAMPLE 250

2-(3,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



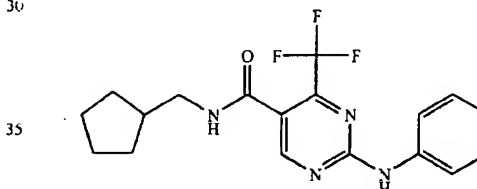
In a manner similar to Reference Example 1(c) 2-(3,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (30 mg) and 4-aminomethyltetrahydropyran (20 mg, ex CombiBlocks) afforded the title compound (38 mg).

NMR (DMSO-d₆) δ 1.18-1.25 (2H, m), 1.62 (2H, d), 1.74 (1H, m), 3.1 (2H, t), 3.25 (2H, m), 3.85 (2H, d), 7.60 (1H, t), 7.69 (1H, m), 8.16 (1H, dd), 8.64 (1H, t), 8.84 (1H, s), 10.70 (1H, s)

LC/MS, t_r 3.45 min. Molecular ion observed (MH⁺) = 449 consistent with the molecular formula C₁₈H₁₇N₄O₂³⁵Cl₂F₃

EXAMPLE 251

2-(Phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclopentylmethyl-amide



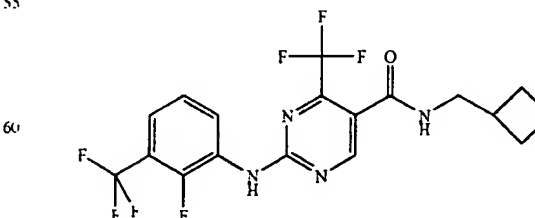
In a manner similar to Reference Example 1 (c), 2-(phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (30 mg) and cyclopentylmethylamine hydrochloride (21 mg) afforded the title compound (32 mg) after purification by trituration with diethylether.

NMR (DMSO-d₆) δ 1.20-1.25 (2H, m), 1.48-1.72 (6H, m), 2.07 (1H, m), 3.13 (2H, t), 7.04 (1H, t), 7.34 (2H, t), 7.74 (2H, d), 8.58 (1H, t), 8.70 (1H, s), 10.35 (1H, s)

LC/MS, t_r 3.52 min, Molecular ion observed (MH⁺) = 365 consistent with the molecular formula C₁₈H₁₉N₄OF₃

EXAMPLE 252

2-(2-Fluoro-3-trifluoromethyl-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



2-Chloro-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide (200 mg) in 2-fluoro-3-trifluoromethyl-

US 7,635,701 B2

147

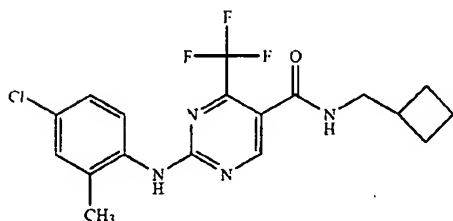
ethyl)aniline (0.5 ml) was heated at 180° C. under microwave irradiation for 30 minutes. The residue was dissolved in dichloromethane and purified over silica gel (Merck 9385) using the Biotage Horizon system eluting with 10% ethylacetate/isohehexane to 100% ethyl acetate gradient to afford the title compound.

NMR (CDCl₃) δ 1.70-1.81 (2H, m), 1.86-2.00 (2H, m), 2.07-2.17 (2H, m), 2.51-2.65 (1H, m), 3.48 (2H, dd), 5.78-5.86 (1H, m), 7.25-7.36 (2H, m), 7.70-7.76 (1H, bs), 8.64-8.72 (1H, m), 8.75-8.79 (1H, s)

LC/MS. t=3.64 min. Molecular ion observed (MH⁺)=437 consistent with the molecular formula C₁₈H₁₃F₇N₄O

EXAMPLE 253

2-(2-Methyl-4-chloro-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid cyclobutylmethyl-amide



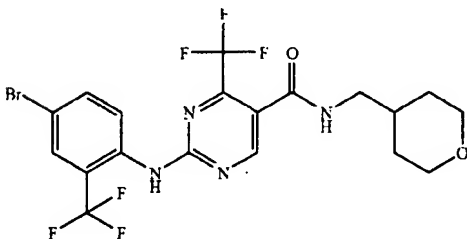
To a solution of 2-chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid cyclobutylmethyl-amide (50 mg) in 1,4-dioxan (1.0 ml) was added 2-methyl-4-chloroaniline (120 mg) and the solution heated at 180° C. under microwave irradiation for 30x2 minutes. The residue was dissolved in 1:1 DMSO: methanol (11.0 ml) and purified by Mass Directed Auto-Purification to afford the title compound (36 mg).

NMR (CDCl₃) δ 1.79-1.80 (2H, m), 1.85-1.99 (2H, m), 2.05-2.16 (2H, m), 2.25-2.63 (1H, m), 5.74-5.83 (1H, m), 7.15 (1H, bs), 7.2-7.78 (2H, m), 7.81 (1H, d), 8.66 (1H, s)

LC/MS. t=3.6 min. Molecular ion observed (MH⁺)=398 consistent with the molecular formula C₁₈H₁₈ClF₃N₄O

EXAMPLE 254

2-(2-Trifluoromethyl-4-bromo-phenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide



2-Chloro-4-trifluoromethyl-pyrimidin-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide (80 mg) in 2-trifluoromethyl-4-bromoaniline (0.5 ml) was heated at 190° C.

148

under microwave irradiation for 20 minutes. The sample was purified by mass directed auto-purification to afford the title compound (21 mg).

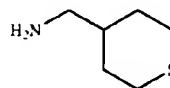
NMR (DMSO-d₆) δ 1.15-1.23 (2H, m), 1.57 (2H, d), 1.60 (1H, m), 3.09 (2H, t), 3.26 (2H, t), 3.84 (2H, d), 7.51 (1H, d), 7.95 (2H, m), 8.58 (2H, s,t), 10.00 (1H, s)

LC/MS. t=3.41 min. Molecular ion observed (MH⁺)=529 consistent with the molecular formula C₁₉H₁₇N₄O₂F₆⁸¹Br

EXAMPLE 255

2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydrothiopyran-4-ylmethyl)-amide

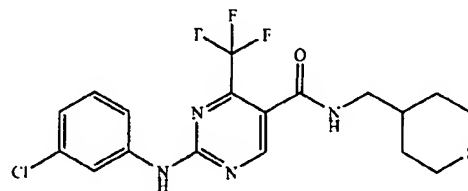
a) 4-(Aminomethyl)tetrahydrothiopyran



A solution of borane-tetrahydrofuran complex (1M in tetrahydrofuran, 11 ml) was added over 5 minutes to a solution of tetrahydro-2H-thiopyran-4-carbonitrile (1.27 g) [Heimgartner et al. *Helv. Chim. Acta* 80(5), 1528 (1997)] in dry tetrahydrofuran (5 ml) under nitrogen at room temperature. The solution was heated at reflux overnight, then cooled to 20° C. Methanol (15 ml) was added dropwise keeping the temperature below 25° C., then the mixture was cooled to 0° C. and dry hydrogen chloride was bubbled through for 15 mins. The resulting mixture was heated at reflux for 1.5 hours, evaporated and the residue re-evaporated twice from methanol. Ether (30 ml) was added giving a white oily solid. The ether was decanted and the residue was dissolved in water (30 ml) and extracted with dichloromethane (2x30 ml). The remaining aqueous was made strongly basic with sodium hydroxide and extracted with dichloromethane (2x30 ml). The combined extracts were dried over potassium carbonate and evaporated to give the title compound (390 mg)

NMR (DMSO) δ 1.2 (5H, m), 2.0 (2H, m), 2.36 (2H, m), 2.55 (4H, m).

b) 2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (tetrahydrothiopyran-4-ylmethyl)-amide



In a manner similar to Reference Example 1b) 2-(3-chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (95 mg) and 4-aminomethyl)tetrahydrothiopyran (79 mg) (above) gave the title compound (92 mg).

NMR (DMSO-d₆) δ 1.26 (2H, m), 1.55 (1H, m), 2.01 (2H, m), 2.60 (4H, m), 3.10 (2H, t), 7.09 (1H, m), 7.37 (1H, t), 7.65 (1H, m), 7.96 (1H, m), 8.63 (1H, t), 8.81 (1H, s), 10.6 (1H, s).

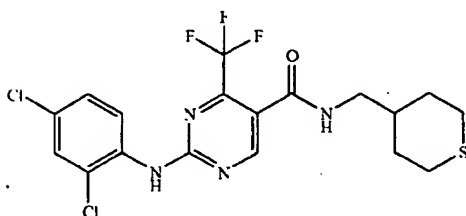
US 7,635,701 B2

149

LC/MS CF111437, $t_r=3.61$ min. Molecular ion observed (MH^+)=431 consistent with the molecular formula $C_{18}H_{18}^{35}ClF_3N_4O_3S$

EXAMPLE 256

2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydrothiopyran-4-ylmethyl)-amide



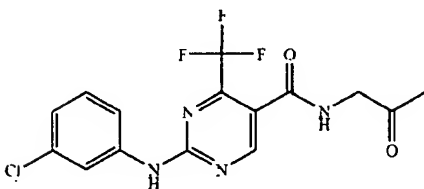
In a manner similar to Reference Example 1b) 2-(2,4-dichlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (106 mg) and 4-(aminomethyl)tetrahydrothiopyran (79 mg) (Example 255a) gave the title compound (82 mg).

NMR (DMSO- d_6) δ 1.27 (2H, m), 1.55 (1H, m), 2.00 (2H, m), 2.59 (4H, m), 3.08 (2H, t), 7.47 (1H, m), 7.57 (1H, d), 7.72 (1H, m), 8.59 (1H, t), 8.64 (1H, s), 10.0 (1H, s).

LC/MS CF111493, $t_r=3.70$ min. Molecular ion observed (MH^+)=465 consistent with the molecular formula $C_{18}H_{17}^{35}Cl_2F_3N_4O_3S$

EXAMPLE 263

2-(3-Chlorophenylamino)-4-trifluoromethyl-pyrimidine-5-carboxylic acid (2-oxo-propyl)-amide



To a stirred solution of 2-(3-chloro-phenylamino)-trifluoromethyl-pyrimidine-5-carboxylic acid (2-hydroxy-propyl)-amide (200 mg) in dimethylsulfoxide (6.0 ml) and trichloramine (324 mg) at 0° C. was added a solution of sulphur trioxide-pyridine complex (250 mg) in dimethylsulfoxide (6.0 ml). This was allowed to warm to room temperature and after 2 hours the mixture was diluted with dichloromethane and washed twice with 0.1N hydrochloric acid. The organic layer was dried (Na_2SO_4) and evaporated. The sample was purified by mass directed auto-purification to afford the title compound (91 mg).

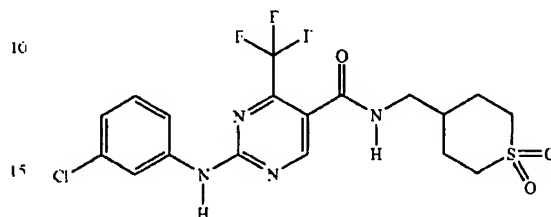
NMR (DMSO- d_6) δ 2.15 (3H, s), 4.13 (2H, d), 7.10 (1H, d), 7.36 (1H, t), 7.67 (1H, d), 7.96 (1H, s), 8.84 (1H, s), 8.94 (1H, t), 10.55 (1H, s)

LC/MS, $t_r=3.18$ min. Molecular ion observed (MH^+)=373 consistent with the molecular formula $C_{15}H_{12}N_4O_2F_3^{34}Cl$

150

EXAMPLE 264

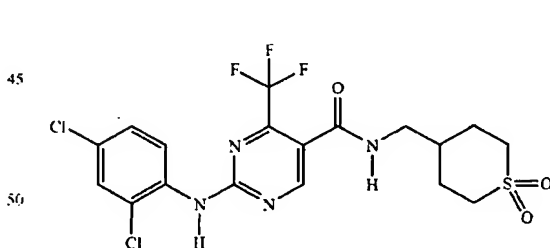
2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (dioxo-hexahydro-11 β -thiopyran-4-ylmethyl)-amide



2-(3-Chlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-thiopyran-4-ylmethyl)-amide (Example 255) (82 mg) was dissolved in dichloromethane (15 ml) and cooled in an ice bath. A solution of 3-chloroperbenzoic acid (95 mg; Lancaster 50-56%) in dichloromethane (5 ml) was added dropwise over 5 mins. The resulting solution was stirred at room temp for 2 hrs then a saturated solution of sodium sulphite (10 ml) was added and the mixture was stirred for 15 mins. Dichloromethane (20 ml), saturated sodium bicarbonate solution (20 ml) and water (30 ml) were added, separated and the organics were washed with water (2x30 ml), dried over magnesium sulphate and evaporated to an oil. Purification by chromatography on silica gel (dichloromethane/methanol 10:1) gave the title compound (17 mg). LC/MS $t_r=3.09$ min, Molecular ion observed (MH^+)=463 consistent with the molecular formula $C_{18}H_{18}^{35}ClF_3N_4O_3S$

EXAMPLE 265

2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (dioxo-hexahydro-11 β -thiopyran-4-ylmethyl)-amide



In a similar manner to Example 264, 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydro-thiopyran-4-ylmethyl)-amide (Example 256) (72 mg) and 3-chloroperbenzoic acid (146 mg) gave the title compound (63 mg)

LC/MS $t_r=3.21$ min. Molecular ion observed (MH^+)=497 consistent with the molecular formula $C_{18}H_{17}^{35}Cl_2F_3N_4O_3S$

EXAMPLE 266

Preparation of Nanomilled Compound

2.5 g of compound of example 176 was weighed into a 10 ml centrifuge tube. 25 ml of 0.3 mM yttrium zirconium (YTZ)

US 7,635,701 B2

151

ceramic milling beads (Manufacturer: Tosoh, Japan: Supplier: Glen Creston Ltd., batch no. 5280130030) was weighed into a 50 ml milling pot. 22.5 ml of aqueous 1.5% HPMC was measured with a measuring cylinder into a 100 ml beaker. This solution was homogenised for 3 seconds with an Ultra Turrax T25 homogeniser. Approximately 200 mg of the 2.5 g of the compound was added to the HPMC solution and homogenised at the lowest speed setting until the powder was wetted. This was repeated until all the compound had been added. The speed of the homogeniser was then increased to maximum and the suspension was homogenised for a further 3 minutes. This suspension was allowed to stand for 30 minutes in order to allow some of the foam to disperse. The suspension was then poured into the 50 ml pot containing the YTZ milling beads, stirring to release any trapped air. The lid to the pot was then fitted and the pot sealed with some Nescro film. This procedure was repeated for a second 50 ml nanomilling pot and both pots were placed on a Retsch mill and milled for a total of 8 hours.

The milling pots were removed from the Retsch mill and left to cool and for the foam to disperse overnight. In the morning the suspension and bead mixture was passed through a 200 μ , 40 mm diameter screen. The contents from each 50 ml pot was washed with aqueous 1.5% HPMC: 10% of the original suspension volume (i.e. 2.5 ml). The suspension from the 2 pots was combined to make 1 batch. The suspension obtained from the method above was named the concentrate.

A sample of the concentrate was diluted 1 in 4 with aqueous 1.5% HPMC to give a nominal concentration of 25 mg/ml. This first dilution was assayed by HPLC. The concentration of the concentrate was calculated to be 91.21 mg/ml.

HPLC Conditions

Column: Symmetry C₁₈ 5 μ 3.9x150 mm column; flow rate 1.0 ml/min; column temp 40° C : UV detection at 280 nm.

Mobile phase gradient: A: water+0.1% trifluoro acetic acid (TFA)

B: acetonitrile+0.1% TFA

TABLE A

HPLC gradient		
Time (min)	A (%)	B (%)
0	90	10
15	10	90
20	10	90
20.1	90	10
30	90	10

A particle size analysis was carried out on the Lecotrac laser particle size analyser. The results are shown in Table B along with the results from the starting material for comparison:

TABLE B

Particle Size Analysis				
Compound	Pre-nanomilling		Post-nanomilling	
	50% percentile (μ)	95% percentile (μ)	50% percentile (μ)	95% percentile (μ)
Example 176	13.15	68.7	0.33	1.78

152

A dilution of nominally 15.0 mg/ml was prepared using 21.36 ml of the concentrate and (100-20.34)ml=83.64 ml of diluent (aqueous 1.5% HPMC).

Compounds of Examples 19, 34, 194, 217, 228, 247 were nanomilled on a 1 g scale using the process described above and the particle size analysed pre and post nanomilling. The results are given in Table C.

TABLE C

Compound	Pre-nanomilling		Post-nanomilling	
	50% percentile (μ)	95% percentile (μ)	50% percentile (μ)	95% percentile (μ)
Ex 247	13.2	68.7	0.64	2.53
Ex 217	5.70	34.9	0.34	1.30
Ex 19	5.22	25.5	0.40	1.40
	4.65	47.1	0.44	1.69
	6.78	33.7	0.56	1.97
	10.46	32.7	0.18	0.56

Formulations for pharmaceutical use incorporating compounds of the present invention either pre or post nanomilling can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

EXAMPLE 267

Inhalant Formulation

A compound of formula (1) or a pharmaceutically acceptable derivative thereof, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

EXAMPLE 268

Tablet Formulation

Tablets/Ingredients	Per Tablet
1 Active ingredient (Compound of formula (1) or pharmaceutically acceptable derivative)	40 mg
2 Corn Starch	20 mg
3 Alginate acid	20 mg
4 Sodium Alginate	20 mg
5 Mg stearate	1.3 mg

Procedure for Tablet Formulation:

Ingredients 1, 2, 3 and 4 are blended in a suitable mixer/blender. Sufficient water is added portion-wise to the blend with careful mixing after each addition until the mass is of a consistency to permit its conversion to wet granules. The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen. The wet granules are then dried in an oven at 140° F (60° C) until dry. The dry granules are lubricated with ingredient No. 5, and the lubricated granules are compressed on a suitable tablet press.

EXAMPLE 269

Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a

US 7,635,701 B2

153

compound of formula (I) in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur (to 100 ml). The solution is then rendered sterile by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

The invention claimed is:

1. 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide or a pharmaceutically acceptable salt thereof.

2. The compound as claimed in claim 1 in nanoparticulate form.

3. 2-(2,4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide.

4. The compound as claimed in claim 3 in nanoparticulate form.

5 A pharmaceutical composition comprising 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide or a pharmaceutically acceptable salt thereof

6. The pharmaceutical composition as claimed in claim 5 further comprising a pharmaceutical carrier or diluent thereof.

7. The pharmaceutical composition as claimed in claim 6, further comprising a second therapeutic agent.

8. The pharmaceutical composition as claimed in claim 5 wherein the compound is in nanoparticulate form.

9. The pharmaceutical composition as claimed in claim 8 further comprising a pharmaceutical carrier or diluent thereof

10. A pharmaceutical composition comprising 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide.

154

11. The pharmaceutical composition as claimed in claim 10 further comprising a pharmaceutical carrier or diluent thereof.

12 The pharmaceutical composition as claimed in claim 11 further comprising a second therapeutic agent.

13. The pharmaceutical composition as claimed in claim 10 wherein the compound is in nanoparticulate form.

14 The pharmaceutical composition as claimed in claim 13 further comprising a pharmaceutical carrier or diluent thereof.

15. The pharmaceutical composition as claimed in claim 14 further comprising a second therapeutic agent.

16. A method of treating a human or animal subject suffering from pain selected from the group consisting of inflammatory pain, visceral pain, cancer pain, neuropathic pain, post operative pain, acute pain, rheumatoid arthritic pain, and osteoarthritic pain, which comprises administering to said subject a therapeutically effective amount of 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide or a pharmaceutically acceptable salt thereof.

17 The method claimed claim 16 wherein the condition is osteoarthritic pain

18. A method of treating a human or animal subject suffering from an inflammatory bowel disease which comprises administering to said subject a therapeutically effective amount of 2-(2,4-dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid (tetrahydropyran-4-ylmethyl)-amide or a pharmaceutically acceptable salt thereof.

19. The method as claimed claim 18 wherein the inflammatory bowel disease is selected from the group consisting of Crohn's disease and ulcerative colitis.

* * * * *

C
10-1032
JDB

CIVIL COVER SHEET

JS-44
(Rev. 1/95 DC)

I (a) PLAINTIFFS Glaxo Group Limited, d/b/a GlaxoSmithKline	DEFENDANTS HON. DAVID J. KAPPOS, Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office
(b) COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF (EXCEPT IN U.S. PLAINTIFF CASES) <u>99999</u>	COUNTY OF RESIDENCE OF FIRST LISTED DEFENDANT (IN U.S. PLAINTIFF CASES ONLY) _____ NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND
(c) ATTORNEYS (FIRM NAME, ADDRESS, AND TELEPHONE NUMBER) Edmund J. Haughey, III, Esq. (DC Bar No. 462773) FITZPATRICK, CELLA, HARPER & SCINTO 975 F Street, N.W. Washington, DC 20004 (202) 530-1010	Case: 1:10-cv-01032 Assigned To: Bates, John D. Assign. Date: 6/18/2010 Description: Admn Agency Review

II. BASIS OF JURISDICTION (PLACE AN X IN ONE BOX ONLY)	III. CITIZENSHIP OF PRINCIPAL PARTIES (PLACE AN X IN ONE BOX FOR PLAINTIFF AND ONE BOX FOR DEFENDANT) <u>FOR DIVERSITY CASES ONLY:</u>																								
<input type="radio"/> 1 U.S. Government Plaintiff <input checked="" type="radio"/> 2 U.S. Government Defendant <input type="radio"/> 3 Federal Question (U.S. Government Not a Party) <input type="radio"/> 4 Diversity (Indicate Citizenship of Parties in item III)	<table style="width: 100%;"> <thead> <tr> <th></th> <th>PTF</th> <th>DFT</th> <th></th> <th>PTF</th> <th>DFT</th> </tr> </thead> <tbody> <tr> <td>Citizen of this State</td> <td><input type="radio"/> 1</td> <td><input type="radio"/> 1</td> <td>Incorporated or Principal Place of Business in This State</td> <td><input type="radio"/> 4</td> <td><input type="radio"/> 4</td> </tr> <tr> <td>Citizen of Another State</td> <td><input type="radio"/> 2</td> <td><input type="radio"/> 2</td> <td>Incorporated and Principal Place of Business in Another State</td> <td><input type="radio"/> 5</td> <td><input type="radio"/> 5</td> </tr> <tr> <td>Citizen or Subject of a Foreign Country</td> <td><input type="radio"/> 3</td> <td><input type="radio"/> 3</td> <td>Foreign Nation</td> <td><input type="radio"/> 6</td> <td><input type="radio"/> 6</td> </tr> </tbody> </table>		PTF	DFT		PTF	DFT	Citizen of this State	<input type="radio"/> 1	<input type="radio"/> 1	Incorporated or Principal Place of Business in This State	<input type="radio"/> 4	<input type="radio"/> 4	Citizen of Another State	<input type="radio"/> 2	<input type="radio"/> 2	Incorporated and Principal Place of Business in Another State	<input type="radio"/> 5	<input type="radio"/> 5	Citizen or Subject of a Foreign Country	<input type="radio"/> 3	<input type="radio"/> 3	Foreign Nation	<input type="radio"/> 6	<input type="radio"/> 6
	PTF	DFT		PTF	DFT																				
Citizen of this State	<input type="radio"/> 1	<input type="radio"/> 1	Incorporated or Principal Place of Business in This State	<input type="radio"/> 4	<input type="radio"/> 4																				
Citizen of Another State	<input type="radio"/> 2	<input type="radio"/> 2	Incorporated and Principal Place of Business in Another State	<input type="radio"/> 5	<input type="radio"/> 5																				
Citizen or Subject of a Foreign Country	<input type="radio"/> 3	<input type="radio"/> 3	Foreign Nation	<input type="radio"/> 6	<input type="radio"/> 6																				

IV. CASE ASSIGNMENT AND NATURE OF SUIT

(Place a X in one category, A-N, that best represents your cause of action and one in a corresponding Nature of Suit)

<input type="radio"/> A. Antitrust <input type="checkbox"/> 410 Antitrust	<input type="radio"/> B. Personal Injury/Malpractice <input type="checkbox"/> 310 Airplane <input type="checkbox"/> 315 Airplane Product Liability <input type="checkbox"/> 320 Assault, Libel & Slander <input type="checkbox"/> 330 Federal Employers Liability <input type="checkbox"/> 340 Marine <input type="checkbox"/> 345 Marine Product Liability <input type="checkbox"/> 350 Motor Vehicle <input type="checkbox"/> 355 Motor Vehicle Product Liability <input type="checkbox"/> 360 Other Personal Injury <input type="checkbox"/> 362 Medical Malpractice <input type="checkbox"/> 365 Product Liability <input type="checkbox"/> 368 Asbestos Product Liability	<input checked="" type="radio"/> C. Administrative Agency Review <input type="checkbox"/> 151 Medicare Act Social Security: <input type="checkbox"/> 861 HIA ((139510) <input type="checkbox"/> 862 Black Lung (923) <input type="checkbox"/> 863 DIWC/DIWW (405(g) <input type="checkbox"/> 864 SSID Title XVI <input type="checkbox"/> 865 RSI (405(g) Other Statutes <input type="checkbox"/> 891 Agricultural Acts <input type="checkbox"/> 892 Economic Stabilization Act <input type="checkbox"/> 893 Environmental Matters <input type="checkbox"/> 894 Energy Allocation Act <input checked="" type="checkbox"/> 890 Other Statutory Actions (If Administrative Agency is Involved)	<input type="radio"/> D. Temporary Restraining Order/Preliminary Injunction Any nature of suit from any category may be selected for this category of case assignment. *(If Antitrust, then A governs)*
<input type="radio"/> E. General Civil (Other) OR <input type="radio"/> F. Pro Se General Civil			
Real Property <input type="checkbox"/> 210 Land Condemnation <input type="checkbox"/> 220 Foreclosure <input type="checkbox"/> 230 Rent, Lease & Ejectment <input type="checkbox"/> 240 Easements to Land <input type="checkbox"/> 245 Tort Product Liability <input type="checkbox"/> 290 All Other Real Property Personal Property <input type="checkbox"/> 370 Other Fraud <input type="checkbox"/> 371 Truth in Lending <input type="checkbox"/> 380 Other Personal Property Damage <input type="checkbox"/> 385 Property Damage Product Liability	Bankruptcy <input type="checkbox"/> 422 Appeal 28 USC 158 <input type="checkbox"/> 423 Withdrawal 28 USC 157 Prisoner Petitions <input type="checkbox"/> 535 Death Penalty <input type="checkbox"/> 540 Mandamus & Other <input type="checkbox"/> 550 Civil Rights <input type="checkbox"/> 555 Prison Condition Property Rights <input type="checkbox"/> 820 Copyrights <input type="checkbox"/> 830 Patent <input type="checkbox"/> 840 Trademark Federal Tax Suits <input type="checkbox"/> 870 Taxes (US plaintiff or defendant) <input type="checkbox"/> 871 IRS-Third Party 26 USC 7609	Forfeiture/Penalty <input type="checkbox"/> 610 Agriculture <input type="checkbox"/> 620 Other Food & Drug <input type="checkbox"/> 625 Drug Related Seizure of Property 21 USC 881 <input type="checkbox"/> 630 Liquor Laws <input type="checkbox"/> 640 RR & Truck <input type="checkbox"/> 650 Airline Regs <input type="checkbox"/> 660 Occupational Safety/Health <input type="checkbox"/> 690 Other Other Statutes <input type="checkbox"/> 400 State Reapportionment <input type="checkbox"/> 430 Banks & Banking <input type="checkbox"/> 450 Commerce/ICC Rates/etc. <input type="checkbox"/> 460 Deportation	<input type="checkbox"/> 470 Racketeer Influenced & Corrupt Organizations <input type="checkbox"/> 480 Consumer Credit <input type="checkbox"/> 490 Cable/Satellite TV <input type="checkbox"/> 810 Selective Service <input type="checkbox"/> 850 Securities/Commodities/Exchange <input type="checkbox"/> 875 Customer Challenge 12 USC 3410 <input type="checkbox"/> 900 Appeal of fee determination under equal access to Justice <input type="checkbox"/> 950 Constitutionality of State Statutes <input type="checkbox"/> 890 Other Statutory Actions (if not administrative agency review or Privacy Act)

3

<input type="radio"/> G. Habeas Corpus/ 2255 <input type="checkbox"/> 530 Habeas Corpus-General <input type="checkbox"/> 510 Motion/Vacate Sentence	<input type="radio"/> H. Employment Discrimination <input type="checkbox"/> 442 Civil Rights-Employment (criteria: race, gender/sex, national origin, discrimination, disability age, religion, retaliation) *(If pro se, select this deck)*	<input type="radio"/> I. FOIA/PRIVACY ACT <input type="checkbox"/> 895 Freedom of Information Act <input type="checkbox"/> 890 Other Statutory Actions (if Privacy Act) *(If pro se, select this deck)*	<input type="radio"/> J. Student Loan <input type="checkbox"/> 152 Recovery of Defaulted Student Loans (excluding veterans)
<input type="radio"/> K. Labor/ERISA (non-employment) <input type="checkbox"/> 710 Fair Labor Standards Act <input type="checkbox"/> 720 Labor/Mgmt. Relations <input type="checkbox"/> 730 Labor/Mgmt. Reporting & Disclosure Act <input type="checkbox"/> 740 Labor Railway Act <input type="checkbox"/> 790 Other Labor Litigation <input type="checkbox"/> 791 Empl. Ret. Inc. Security Act	<input type="radio"/> L. Other Civil Rights (non-employment) <input type="checkbox"/> 441 Voting (if not Voting Rights Act) <input type="checkbox"/> 443 Housing/Accommodations <input type="checkbox"/> 444 Welfare <input type="checkbox"/> 440 Other Civil Rights <input type="checkbox"/> 445 American w/Disabilities-Employment <input type="checkbox"/> 446 Americans w/Disabilities-Other	<input type="radio"/> M. Contract <input type="checkbox"/> 110 Insurance <input type="checkbox"/> 120 Marine <input type="checkbox"/> 130 Miller Act <input type="checkbox"/> 140 Negotiable Instrument <input type="checkbox"/> 150 Recovery of Overpayment & Enforcement of Judgment <input type="checkbox"/> 153 Recovery of Overpayment of Veteran's Benefits <input type="checkbox"/> 160 Stockholder's Suits <input type="checkbox"/> 190 Other Contracts <input type="checkbox"/> 195 Contract Product Liability <input type="checkbox"/> 196 Franchise	<input type="radio"/> N. Three-Judge Court <input type="checkbox"/> 441 Civil Rights-Voting (if Voting Rights Act)

V. ORIGIN

- ☒ 1 Original Proceeding
 ☐ 2 Removed from State Court
 ☐ 3 Remanded from Appellate Court
 ☐ 4 Reinstated or Reopened
 ☐ 5 Transferred from another district (specify)
 ☐ 6 Multi-district Litigation
 ☐ 7 Appeal to District Judge from Mag. Judge

VI. CAUSE OF ACTION (CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE A BRIEF STATEMENT OF CAUSE.)

35 U.S.C. Section 154, request for correction of patent term adjustment

VII. REQUESTED IN COMPLAINT
 CHECK IF THIS IS A CLASS ACTION UNDER I.R.C.P. 23 ☐

DEMAND \$

JURY DEMAND:

Check YES only if demanded in complaint

YES ☐NO ☒**VIII. RELATED CASE(S) IF ANY**

(See instruction)

YES ☐NO ☒

If yes, please complete related case form

DATE

6/18/10

SIGNATURE OF ATTORNEY OF RECORD

[Signature]**INSTRUCTIONS FOR COMPLETING CIVIL COVER SHEET JS-44**

Authority for Civil Cover Sheet

The JS-44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. Listed below are tips for completing the civil cover sheet. These tips coincide with the Roman Numerals on the Cover Sheet.

- I.** COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF/DEFENDANT (b) County of residence. Use 11001 to indicate plaintiff is resident of Washington, D.C., 88888 if plaintiff is resident of the United States but not of Washington, D.C., and 99999 if plaintiff is outside the United States.
- III.** CITIZENSHIP OF PRINCIPAL PARTIES. This section is completed only if diversity of citizenship was selected as the Basis of Jurisdiction under Section II.
- IV.** CASE ASSIGNMENT AND NATURE OF SUIT. The assignment of a judge to your case will depend on the category you select that best represents the primary cause of action found in your complaint. You may select only one category. You must also select one corresponding nature of suit found under the category of case.
- VI.** CAUSE OF ACTION. Cite the US Civil Statute under which you are filing and write a brief statement of the primary cause.
- VIII.** RELATED CASES, IF ANY. If you indicated that there is a related case, you must complete a related case form, which may be obtained from the Clerk's Office.

Because of the need for accurate and complete information, you should ensure the accuracy of the information provided prior to signing the form.